THE AMERICAN JOURNAL OF PSYCHIATRY

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Presidential Papers: 1990

Family Functioning and Major Depression: An Overview
By Gabor I. Keitner and Ivan W. Miller

THE AMERICAN JOURNAL OF PSYCHIATRY

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Volume 147, Number 9   September 1990

New Policy of Structured Abstracts

Effective with the January 1991 issue, *The American Journal of Psychiatry* will institute a policy of structured abstracts for Special Articles and Regular Articles. Authors of Special Articles must include the following key information: purpose (the primary objective of the review article); data sources (a brief summary of sources); study selection (the number of studies selected for review and how they were selected); data extraction (rules for abstracting data and how they were applied); results of data synthesis (the methods of data synthesis and key results); and key conclusions, including potential applications and research needs. Authors of Regular Articles must include in the abstract the following key information: objective (the questions addressed by the study); design of the study; setting (location and level of clinical care); patients or participants (the manner of selection and number who entered and completed the study); interventions (the exact treatment or intervention, if any); main outcome measures (the primary study outcome measure as planned before data collection began); results (key findings); and key conclusions, including direct clinical applications. Also effective with the January 1991 issue, abstracts for Special Articles and Regular Articles will be increased to a maximum of 250 words and the abstracts for Clinical and Research Reports will be increased to 60 words.

"IT FEELS GOOD TO FEEL USEFUL AGAIN"

For the chronic schizophrenic patient, Navane can mean more competent work performance,[1,2] and a smoother path towards social recovery. Navane may help improve the ability to concentrate, and promote a better attitude toward work and co-workers.[1-3]

Anticholinergic[4] and cardiovascular[5,6] side effects in patients treated with Navane are reported infrequently. Should extrapyramidal symptoms occur, they usually can be controlled.

27% rise in work output compared to baseline shown in patients switched to Navane[2,3]

(Adapted from DiMascio and Demirgian[2,3])

Forty-two psychotic male and female patients under age 55 were entered in this study on a nonblind basis, and randomly assigned to their regular medication or switched to thiothixene. Patients were evaluated at baseline and on a daily basis, and periodically rated on the Global Improvement and Brief Psychiatric Rating Scales.

In schizophrenia,

Navane® (thiothixene)(thiothixene HCl)

Please see brief summary of NAVANE® (thiothixene/thiothixene HCl) prescribing information on adjacent page.

Navane®
(thiothixene) (thiothixene HCl)

It feels good to feel useful again

Capsules

1 mg 2 mg 5 mg 10 mg

20 mg

Intramuscular
2 mg/ml 5 mg/ml

Navane
thiothixene HCl
CONCENTRATE
5 mg/ml
30 ml
ROERIG

Concentrate
5 mg/ml

References: 1. Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2. DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3. DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association. Washington, DC, May 3-6, 1971. 4. Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry.* Basel, Switzerland, S. Karger, 1969, vol 2, pp 45-52. 5. Dillenkoffer RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of the American Psychiatric Association, Dallas, May 1-4, 1972. 6. Data available on request from Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml
Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.
Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.
Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)
Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.
Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)
Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.
Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).
Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.
Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.
Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, have occurred occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.
Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.
Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.
Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

ROERIG *Pfizer*

A division of Pfizer Pharmaceuticals
New York, New York 10017

Coming in the October 1990 issue of

THE AMERICAN JOURNAL OF PSYCHIATRY

Turning Points in Twentieth-Century American Psychiatry
By Melvin Sabshin

Evidence of the Role of Psychosocial Factors in Diabetes Mellitus: A Review
By Jean W. Helz and Bryce Templeton

Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.

NOVEMBER

November 4–6, 7th Annual Conference, The Chronic Patient: Care and Treatment, "Issues and Challenges in the 90's," Jacksonville. Contact Ed R. Paat, M.S., University Medical Center, Community Mental Health Center, 655 West 8th Street, Jacksonville, FL 32209; 904-350-6806.

November 6–10, annual meeting, World Association for Social Psychiatry, Washington, DC. Contact John L. Carleton, M.D., 696 Ladera Lane, Santa Barbara, CA 93108-1622; 805-969-1376.

November 8–10, annual meeting, Association for Retarded Citizens of the United States, Tampa, Florida. Contact Alan Abeson, Ed.D., Executive Director, 2501 Avenue J, Arlington, TX 76006; 817-640-0204.

November 11–14, 2nd International Congress on Disorders of Personality, Miami. Contact Erik Simonsen, M.D., Nordvang Hospital, DK-2600 Glostrup, Denmark.

November 13–16, annual conference, Association for Medical Education and Research in Substance Abuse, Rockville, Maryland. Contact Susan Paquin Simpson, AMERSA Conference Coordinator, Brown University Center for Alcohol and Addiction Studies, Box G, Providence, RI 02912; 401-863-3173.

November 13–18, annual meeting, National Mental Health Association, Indianapolis. Contact Preston J. Garrison, Executive Director, 1021 Prince Street, Alexandria, VA 22314; 703-684-7722.

November 15–17, annual meeting, American Academy of Medical Administrators, Nashville, Tennessee. Contact

Thomas R. O'Donovan, Ph.D., President, 30555 Southfield Road, Suite 150, Southfield, MI 48076; 313-540-4310.

November 15–18, annual meeting, Academy of Psychosomatic Medicine, Phoenix, Arizona. Contact Evelyne Hallberg, Executive Director, 5824 N. Magnolia, Chicago, IL 60660; 312-784-2025.

November 26–28, International Symposium on Functional Psychiatric Disorders in the Elderly, Melbourne. Contact Associate Professor Edmond Chiu, Department of Psychiatry, St. Vincent's Hospital, Victoria Parade, Fitzroy, Victoria 3065, Australia.

DECEMBER

December 10–15, annual meeting, American College of Neuropsychopharmacology, Maui, Hawaii. Contact Oakley Ray, Ph.D., Secretary, Box 1823-Station B, Nashville, TN 37221; 615-327-7200.

December 11–14, 8th International Psychiatric Conference, Pakistan Psychiatric Society, Islamabad, Pakistan. Contact: Professor Malik H. Mubbashar, Organizing Committee Chair, 8th International Psychiatric Conference, Department of Psychiatry, Rawalpindi General Hospital, Rawalpindi, Pakistan.

December 12–16, annual meeting, Milton H. Erickson Foundation, Inc., Anaheim, California. Contact Jeffrey K. Zeig, Ph.D., Director, 3606 North 24th Street, Phoenix, AZ 85016; 602-956-6196.

Productive Days... Restful Nights and Pamelor® (nortriptyline HCl)

The Full-Time Antidepressant
for patients whose symptoms include insomnia and anxiety

PAMELOR®
(nortriptyline HCl)

CAPSULES: 10 mg, 25 mg, 50 mg, and 75 mg; SOLUTION: 10 mg/5 mL and alcohol 4%

The active metabolite of amitriptyline

**Reduce the risk of
life-style disruptions
that can interfere
with therapy
for depression.**

Start with Wellbutrin to help clear depression with few life-style disruptions.

Relieves depression effectively.
Therapeutically equivalent to amitriptyline with no differences in the frequency, degree, or rate of response.[1]

Little or no daytime drowsiness.
Patients treated with WELLBUTRIN experienced sedation less often than those treated with amitriptyline or doxepin.[2,3]

Few anticholinergic side effects.
Patients experienced troubling side effects, such as dry mouth and constipation, less often than those treated with either doxepin or amitriptyline.[2,3]

No clinically significant effect on cardiac conduction.
No significant changes in any measured ECG parameter. A substantially wider margin of safety than amitriptyline with respect to cardiac conduction.[4]

No clinically significant orthostatic hypotension.
No clinically significant orthostatic hypotension in patients with preexisting cardiac disease or in healthy depressed patients who had experienced orthostatic hypotension when treated with tricyclics.[5,6]

Important Considerations
The most common side effects of WELLBUTRIN are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor. The principal medically important adverse reaction with WELLBUTRIN is seizure, for which the incidence is approximately four-tenths of one percent (4/1,000). This incidence may exceed that of other marketed antidepressants. For more information, see brief summary of full prescribing information on last page of this advertisement, especially the WARNINGS section regarding the incidence of seizures and the recommendations for reducing the risk.

References: 1. Mendels J, Amin MM, Chouinard G, et al. A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry.* 1983;44(5, sec 2):118-120. **2.** Feighner J, Hendrickson G, Miller L, Stern W. Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. *J Clin Psychopharmacol.* 1986;6:27-32. **3.** Data on file, Burroughs Wellcome Co., 1989. **4.** Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry.* 1983;44(5, sec 2):174-175. **5.** Farid FF, Wenger TL, Tsai SY, Singh BN, Stern WC. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. *J Clin Psychiatry.* 1983;44(5, sec 2):170-173. **6.** Roose SP, Glassman AH, Giardina EGV, Johnson LL, Walsh BT, Bigger JT Jr. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. *J Clin Psychopharmacol.* 1987;7:247-251.

Feeling better
Living better

Wellbutrin®
(BUPROPION HCl)

See brief summary of full prescribing information on last page of this advertisement.

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Wellbutrin is indicated for the treatment of depression. A physician considering the initiation of Wellbutrin should be aware that the drug may cause generalized seizures with an approximate incidence of 0.4% (4/1000). This incidence may exceed that of other antidepressants as much as fourfold. This relative risk is only an approximation since no direct comparative studies have been conducted.

CONTRAINDICATIONS: Wellbutrin is contraindicated in patients: with a seizure disorder; with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in such patients; who have shown an allergic response to it; or who are currently being treated with an MAO inhibitor. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

WARNINGS: SEIZURES: Wellbutrin is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the pre-approval evaluation period, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight (8) seizures occurred during the initial 8 week treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

Recommendations for reducing the risk of seizure: Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if (1) the total daily dose of Wellbutrin does *not* exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose *not* to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when Wellbutrin is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

PRECAUTIONS: General:

Agitation and Insomnia: A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

Use in Patients with Systemic Illness: There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups.

Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients: Consult complete product information.

Drug Interactions: No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.

However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution. Low initial dosing and small gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality.) There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of Wellbutrin on labor and delivery in humans is unknown.

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of Wellbutrin in individuals under 18 years old have not been established.

Use in the Elderly: Wellbutrin has not been systematically evaluated in older patients.

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in the product's pre-approval clinical trials. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600 mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in the WARNINGS and PRECAUTIONS sections.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)	Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)
CARDIOVASCULAR			Dry Mouth	27.6	18.4
Cardiac Arrhythmias	5.3	4.3	Excessive Sweating	22.3	14.6
Dizziness	22.3	16.2	Headache/Migraine	25.7	22.2
Hypertension	4.3	1.6	Impaired Sleep Quality	4.0	1.6
Hypotension	2.5	2.2	Increased Salivary Flow	3.4	3.8
Palpitations	3.7	2.2	Insomnia	18.6	15.7
Syncope	1.2	0.5	Muscle Spasms	1.9	3.2
Tachycardia	10.8	8.6	Pseudoparkinsonism	1.5	1.6
DERMATOLOGIC			Sedation	19.8	19.5
Pruritus	2.2	0.0	Sensory Disturbance	4.0	3.2
Rash	8.0	6.5	Tremor	21.1	7.6
GASTROINTESTINAL			**NEUROPSYCHIATRIC**		
Anorexia	18.3	18.4	Agitation	31.9	22.2
Appetite Increase	3.7	2.2	Anxiety	3.1	1.1
Constipation	26.0	17.3	Confusion	8.4	4.9
Diarrhea	6.8	8.6	Decreased Libido	3.1	1.6
Dyspepsia	3.1	2.2	Delusions	1.2	1.1
Nausea/Vomiting	22.9	18.9	Disturbed Concentration	3.1	3.8
Weight Gain	13.6	22.7	Euphoria	1.2	0.5
Weight Loss	23.2	23.2	Hostility	5.6	3.8
GENITOURINARY			**NONSPECIFIC**		
Impotence	3.4	3.1	Fatigue	5.0	8.6
Menstrual Complaints	4.7	1.1	Fever/Chills	1.2	0.5
Urinary Frequency	2.5	2.2	**RESPIRATORY**		
Urinary Retention	1.9	2.2	Upper Respiratory Complaints	5.0	11.4
MUSCULOSKELETAL					
Arthritis	3.1	2.7	**SPECIAL SENSES**		
NEUROLOGICAL			Auditory Disturbance	5.3	3.2
Akathisia	1.5	1.1	Blurred Vision	14.6	10.3
Akinesia/Bradykinesia	8.0	8.6	Gustatory Disturbance	3.1	1.1
Cutaneous Temperature Disturbance	1.9	1.1			

*Events reported by at least 1% of Wellbutrin patients are included.

Other events observed during the entire pre-approval evaluation of Wellbutrin: During its pre-approval assessment, Wellbutrin was evaluated in almost 2400 subjects. The conditions and duration of exposure to Wellbutrin varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; and rare were pallor and phlebitis.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color and hirsutism.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, G.I. bleeding, and intestinal perforation.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare was lymphadenopathy.

Neurological: (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; and rare were EEG abnormality, abnormal neurological exam, impaired attention, and sciatica.

Neuropsychiatric: (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis and rate or rhythm disorder.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction and overdose.

Post-Approval Reports: The following additional events were rarely observed (less than 1/1000 patients) post-approval.

Cardiovascular: Flushing and myocardial infarction.

Dermatologic: Acne.

Gastrointestinal: Stomach ulcer.

Hematologic/Oncologic: Anemia and pancytopenia.

Neurological: Aphasia.

Musculoskeletal: Musculoskeletal chest pain.

Respiratory: Pneumonia and pulmonary embolism.

DOSAGE AND ADMINISTRATION: General Dosing Considerations: It is particularly important to administer Wellbutrin in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3 day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

No single dose of Wellbutrin should exceed 150 mg. Wellbutrin should be administered t.i.d., preferably with at least 6 hours between successive doses.

Usual Dosage for Adults: The usual adult dose is 300 mg/day, given t.i.d. Dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg t.i.d., no sooner than 3 days after beginning therapy (see table below).

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of Wellbutrin may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.d. with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. Wellbutrin should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

Elderly Patients: In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs.

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No Surprises

Books Received

Human Behavior in the Social Environment: A Social Systems Approach, 4th ed., by Ralph E. Anderson and Irl Carter. New York, Aldine de Gruyter, 1990, 267 pp., $39.95; $20.95 (paper).

The Personal Nature of Notions of Consciousness: A Theoretical and Empirical Examination of the Role of the Personal in the Understanding of Consciousness, by Imants Baruss. Lanham, Md., University Press of America, 1990, 210 pp., $29.75.

The Year Book of Geriatrics and Gerontology 1990, edited by John C. Beck, M.D., Itamar B. Abrass, M.D., John R. Burton, M.D., Jeffrey L. Cummings, M.D., Takashi Makinodan, Ph.D., and Gary W. Small, M.D. Chicago, Year Book Medical Publishers, 1990, 296 pp., $51.95.

The Freudian Body: Psychoanalysis and Art (1986), by Leo Bersani. New York, Columbia University Press, 1990, 124 pp., $14.50 (paper).

The Practical, Moral, and Personal Sense of Nursing: A Phenomenological Philosophy of Practice, by Anne H. Bishop and John R. Scudder, Jr. Albany, State University of New York Press, 1990, 182 pp., $44.50; $14.95 (paper).

The Management of Pain, 2nd ed., vols. I, II, by John J. Bonica, M.D., D.Sc., D.Med.Sc.(Hon.), F.F.A.R.C.S.(Hon.), with John D. Loeser, M.D., C. Richard Chapman, Ph.D., and Wilbert E. Fordyce, Ph.D. Philadelphia, Lea & Febiger, 1990, 2,120 pp., $225.00.

The Mask of Sanity: An Attempt to Clarify Some Issues About the So-Called Psychopathic Personality, 5th ed. (1976), by Hervey Cleckley, M.D. Augusta, Ga., Emily S. Cleckley, 1988, 462 pp., $21.95.

My Days in Court: Unique Views of the Famous and Infamous by a Court Artist, by Ida Libby Dengrove and Frank W. Martin. New York, William Morrow and Co., 1990, 224 pp., $22.95.

Families and Health Care: Psychosocial Practice, by Kathleen Ell and Helen Northen. New York, Aldine de Gruyter, 1990, 308 pp., $39.95; $18.95 (paper).

Holiday of Darkness: A Psychologist's Personal Journey Out of His Depression, revised ed., by Norman S. Endler. Toronto, Wall & Thompson, 1990, 149 pp., $39.95; $9.95 (paper).

The History of Psychoanalysis, new expanded ed., by Reuben Fine. Northvale, N.J., Jason Aronson, 1990, 731 pp., $40.00.

Suicide Risk: Assessment and Response Guidelines, by William J. Fremouw, Maria de Perczel, and Thomas E. Ellis. New York, Pergamon Press, 1990, 158 pp., $26.00; $14.95 (paper).

Never Be Tired Again! (1988), by Dr. David C. Gardner and Dr. Grace Joely Beatty. New York, Perennial Library (Harper & Row), 1990, 359 pp., $8.95 (paper).

The Work and Play of Winnicott, by Simon A. Grolnick, M.D. Northvale, N.J., Jason Aronson, 1990, 216 pp., $25.00.

Obsessive-Compulsive Disorders: Theory and Management, 2nd ed., edited by Michael A. Jenicke, M.D., Lee Baer, Ph.D., and William E. Minichiello, Ed.D. Chicago, Year Book Medical Publishers, 1990, 425 pp., no price listed.

The Exercise Prescription for Depression and Anxiety, by Keith W. Johnsgård, Ph.D. New York, Plenum, 1989, 312 pp., $22.95.

Women, Sex, and Addiction: A Search for Love and Power (1989), by Charlotte Davis Kasl, Ph.D. New York, Perennial Library (Harper & Row), 1990, 393 pp., $9.95 (paper).

Dementia Disorders: Advances and Prospects, edited by C.L.E. Katona. New York, Chapman and Hall, 1989, 228 pp., $69.95.

Research Agendas in the Sociology of Emotions, edited by Theodore D. Kemper. Albany, State University of New York Press, 1990, 333 pp., $57.50; $18.95 (paper).

The Healing Way: Adult Recovery From Childhood Sexual Abuse, by Kristin A. Kunzman. Center City, Minn., Hazelden, 1990, 146 pp., no price listed (paper).

The Limits of Interpretation (1987), by Peter Lomas. Northvale, N.J., Jason Aronson, 1990, 153 pp., $18.50.

Depression: New Directions in Theory, Research, and Practice, edited by C. Douglas McCann and Norman S. Endler. Toronto, Wall Editions (Wall & Emerson), 1990, 394 pp., $39.95.

Post-Traumatic Stress Disorder: Assessment, Differential Diagnosis, and Forensic Evaluation, edited by Carroll L. Meek, Ph.D. Sarasota, Fla., Professional Resource Exchange, 1990, 215 pp., $32.35.

Inner Natures: Brain, Self and Personality, by Laurence Miller, Ph.D. New York, St. Martin's Press, 1990, 275 pp., $19.95.

Tomorrow's Doctors: The Path to Successful Practice in the 1990s, by Benjamin H. Natelson, M.D. New York, Insight Books (Plenum), 1990, 275 pp., $19.95.

Movement and Dance Education (1973), by Marion North. Plymouth, U.K., Northcote House, 1990, 295 pp., $19.95 (paper).

Personality Assessment Through Movement (1972), by Marion North. Plymouth, U.K., Northcote House, 1990, 207 pp., $19.95 (paper).

The Personality Self-Portrait: Why You Think, Work, Love, and Act the Way You Do, by John M. Oldham, M.D., and Lois B. Morris. New York, Bantam Books, 1990, 426 pp., $18.95.

Counseling and Social Support: Perspectives and Practice, by Richard E. Pearson. Newbury Park, Calif., Sage Publications, 1990, 265 pp., $14.95 (paper).

The Caregivers' Journey: When You Love Someone With AIDS, by Mel Pohl, M.D., Deniston Kay, Ph.D., and Doug Toft. Center City, Minn., Hazelden, 1990, 227 pp., no price listed (paper).

Opioids, Bulimia, and Alcohol Abuse and Alcoholism, edited by Larry D. Reid, Ph.D. New York, Springer-Verlag New York, 1990, 393 pp., no price listed.

A Dissenter in the House of God, by Alvin Rosenfeld. New York, St. Martin's Press, 1990, 200 pp., $15.95.

Turning Points in Analytic Therapy: From Winnicott to Kernberg, by Gerald Schoenwolf, Ph.D. Northvale, N.J., Jason Aronson, 1990, 236 pp., $30.00.

Mammalian Behavior: The Theory and the Science, by John Philip Smith. Tuckahoe, N.Y., Bench Mark Books, 1990, 420 pp., $32.00 (paper).

On Jung, by Anthony Stevens. New York, Routledge, 1990, 281 pp., $22.50.

The Year Book of Psychiatry and Applied Mental Health 1990, edited by John A. Talbott, M.D., Allen Frances, M.D., Richard J. Frances, M.D., Daniel X. Freedman, M.D., Herbert Y. Meltzer, M.D., John E. Schowalter, M.D., and Stuart C. Yudofsky, M.D. Chicago, Year Book Medical Publishers, 1990, 391 pp., $49.95.

Infant Previewing: Predicting and Sharing Interpersonal Outcome, by Paul V. Trad. New York, Springer-Verlag New York, 1990, 271 pp., $54.50.

Panic Disorder: The Great Pretender, by H. Michael Zal, D.O., F.A.C.N. New York, Insight Books (Plenum), 1990, 223 pp., $22.95.

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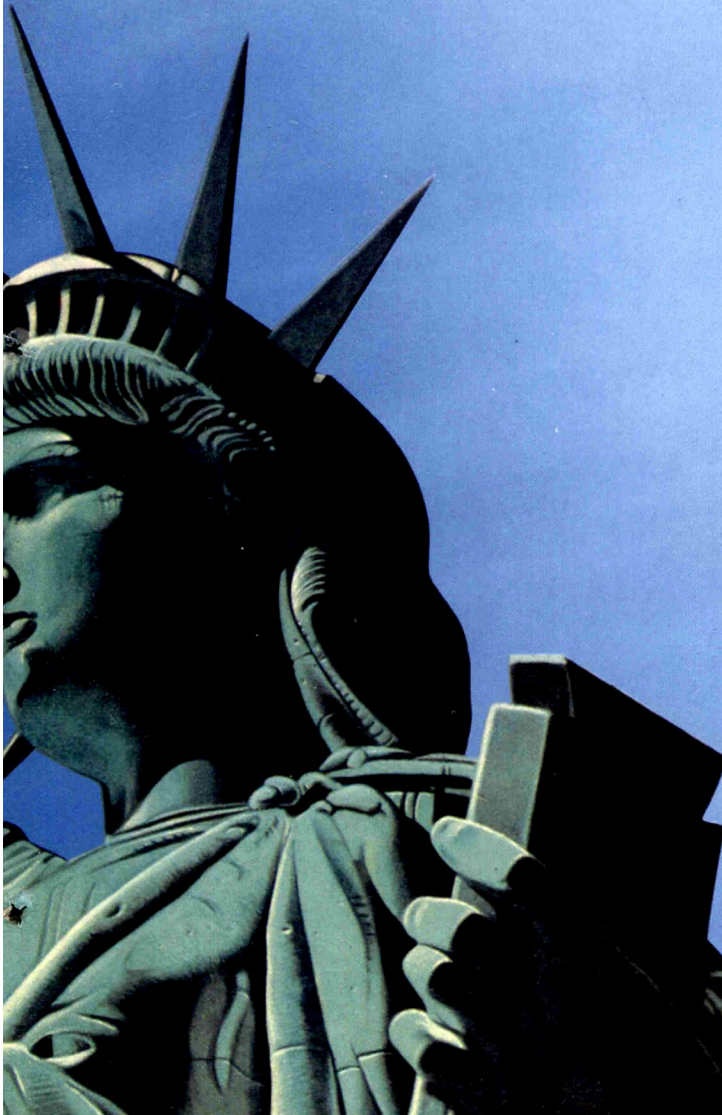
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- CLOZARIL use is associated with a substantial risk of seizure, an apparently dose-dependent reaction affecting 1–2% of patients at low doses (below 300 mg/day), 3–4% at moderate doses, and 5% at high doses (600–900 mg/day)[‡]

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TABLETS

CAUTION: Federal law prohibits dispensing without a prescription.

CONTRAINDICATIONS

CLOZARIL is contraindicated in patients with myeloproliferative disorders, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. CLOZARIL should not be used simultaneously with other agents having a well-known potential to suppress bone marrow function. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

WARNINGS

General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZARIL MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR FOUR WEEKS AFTER THE DISCONTINUATION OF CLOZARIL.

CLOZARIL IS AVAILABLE ONLY THROUGH THE CLOZARIL PATIENT MANAGEMENT SYSTEM℠ (CPMS℠).

Agranulocytosis

Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm³, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1988, 35% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.

Treatment should not be initiated if the WBC count is less than 3500 per mm³, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm³ or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm³, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm³ and a granulocyte count above 1500 per mm³, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000 per mm³ or the granulocyte count below 1500 per mm³, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm³ and the granulocyte count returns to levels above 1500 per mm³. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm³.

If the total WBC count falls below 2000 per mm³ or the granulocyte count falls below 1000 per mm³, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000 per mm³, or granulocyte counts below 1000 per mm³ during CLOZARIL therapy should not be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).

Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.

To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.

Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL

CLOZARIL®

(clozapine)

TABLETS

Drug Interactions

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function. Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs. Because CLOZARIL is highly bound to serum protein, the administration of CLOZARIL to a patient taking another drug which is highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL by other highly bound drugs.

CLOZARIL may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

ADVERSE REACTIONS

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of 5% or greater were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

DOSAGE AND ADMINISTRATION

Initial Treatment

It is recommended that treatment with CLOZARIL begin at 25 mg once or twice daily, and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of two weeks. Subsequent dosage increments should be made no more than once- or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL in treatment resistant patients, the mean and median CLOZARIL doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

Discontinuation of Treatment

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1 to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

CLOZARIL is available only through the Clozaril Patient Management System, a program that combines white blood cell testing, patient monitoring, pharmacy, and drug distribution services, all linked to compliance with required safety monitoring.

To prescribe CLOZARIL call 1-800-237-CPMS (2767) or mail in a completed CPMS Enrollment Form.

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With depression...

In a clinical trial, XANAX was effective in reducing anxiety symptoms associated with moderate to severe depression.*

Patients taking XANAX should be alerted to possible additive CNS depressant effects when it is administered with other medications that produce CNS depression.

The usual starting dosage of XANAX is 0.25 to 0.5 mg t.i.d.

*Data on file. The Upjohn Company
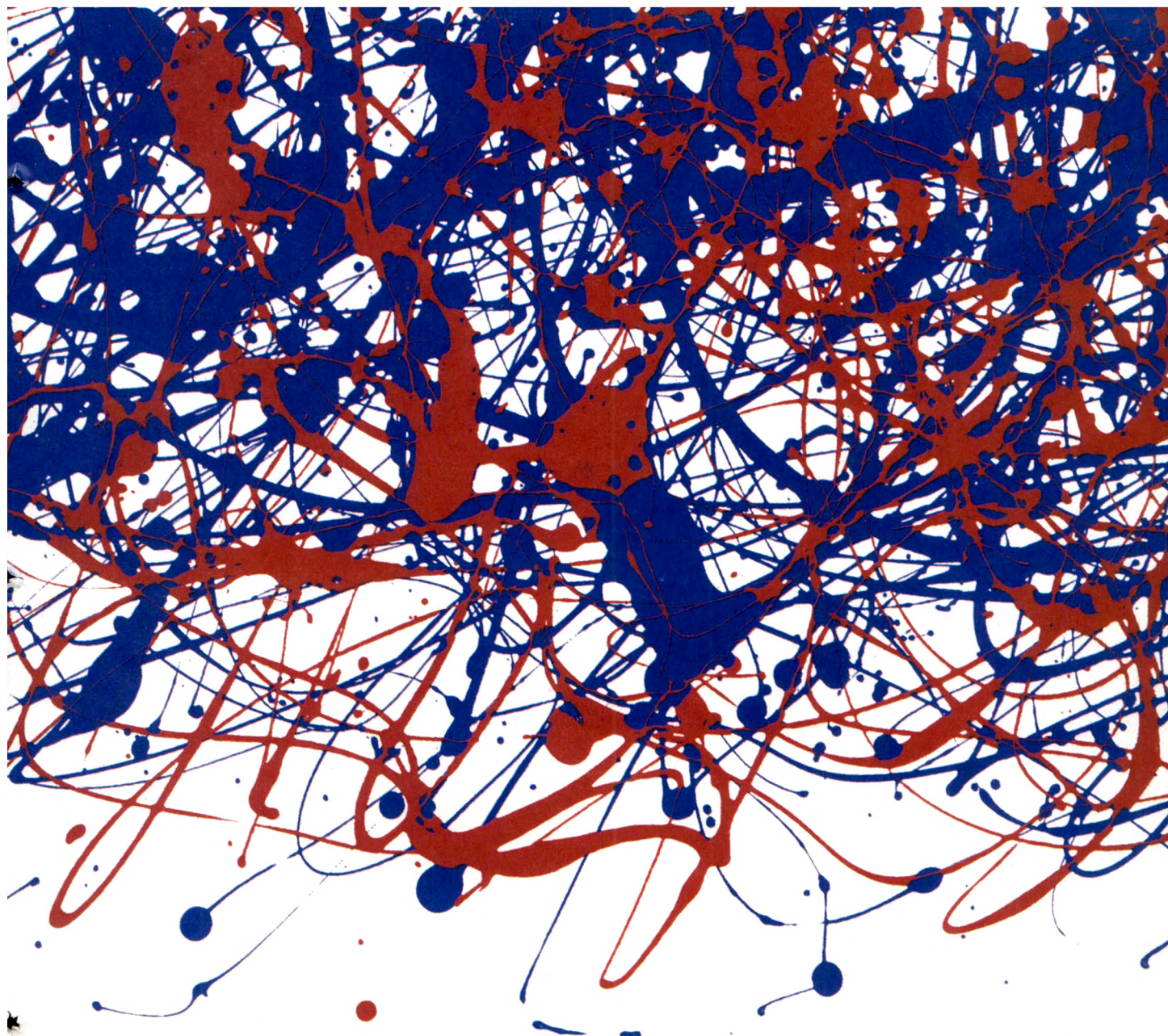
XANAX® Tablets
(alprazolam, ©)

INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions.) Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings.) Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

HALDOL® Decanoate 100
(HALOPERIDOL) INJECTION 100mg/mL

HALDOL® Decanoate 50
(HALOPERIDOL) INJECTION 50mg/mL

For IM Injection Only

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL Decanoate 50 and HALDOL Decanoate 100 are attributed to HALDOL haloperidol as the active medication, Contraindications, Warnings, and additional information are those of HALDOL, modified to reflect the prolonged action.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS—Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS—Drug Interactions)

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women, likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. Withdrawal Emergent Neurological Signs—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. Tardive Dyskinesia—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. Tardive Dystonia—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. Other CNS Effects—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

McNeil Pharmaceutical, McNEILAB, INC., Spring House, PA 19477

8/23/89

Powerful medicine
to stop intrusive thoughts and acts

STOP. AM I LOSING MY MIND? MIND? IT'S SO HARD TO HIDE IT. I JUST
CAN'T ANYMORE. I CAN'T ST OP. AM I LOSING MY MIND? IT'S SO HA
I LOSING MY MIND? IT I JUST CAN'T ANYMORE. I CAN'T STOP.

Anafranil®
clomipramine HCl

Powerful tricyclic therapy for obsessive-compulsive disorder

▲ *Relieves obsessions and compulsions in OCD patients with or without concomitant depression*

Reduces anxiety-producing intrusive thoughts[1]

Reduces ritualized behavior[1]

▲ *Dual mode of action creates a unique treatment role*
Anafranil is believed to block the reuptake of serotonin and norepinephrine.[2,3]

▲ *Safety and tolerability demonstrated in over 20 years of worldwide use*

Symptoms are substantially reduced in 58% of patients.[4]

The most common adverse events are dry mouth, somnolence, tremor, dizziness, constipation, and ejaculatory failure. Anafranil may lower the seizure threshold. See Warnings and full Prescribing Information on page 4.

CIBA–GEIGY

References: 1. DeVeaugh-Geiss J, Landau P, Katz R. Treatment of obsessive-compulsive disorder with clomipramine. Psychiatr Ann. 1989;19:97-101. **2.** Insel TR, Murphy DL, Cohen RM et al. Obsessive-compulsive disorder: A double-blind trial of clomipramine and clorgyline. Arch Gen Psychiatry. 1983;40:605-611. **3.** Zohar J, Insel TR, Zohar-Kadouch RC et al. Serotonergic responsivity in obsessive-compulsive disorder. Arch Gen Psychiatry. 1988;45:167-171. **4.** Data on file, CIBA-GEIGY Corporation.

Anafranil®
clomipramine hydrochloride
Capsules
Prescribing Information

DESCRIPTION

Anafranil, clomipramine hydrochloride, is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Anafranil is available as capsules of 25, 50, and 75 mg for oral administration.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:

$$CH_2CH_2CH_2-N\begin{array}{c}CH_3\\CH_3\end{array}\cdot HCl$$

Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

Inactive Ingredients: D&C Red No. 33 (25-mg capsules only), D&C Yellow No. 10, FD&C Blue No. 1 (50-mg capsules only), FD&C Yellow No. 6, gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch, and titanium dioxide.

CLINICAL PHARMACOLOGY
Pharmacodynamics

Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's relatively selective capacity to inhibit the reuptake of serotonin (5-HT) as compared to norepinephrine (NE) may be important.

Pharmacokinetics

Absorption/Bioavailability: CMI from Anafranil capsules is as bioavailable as CMI from a solution. The bioavailability of CMI from capsules is not significantly affected by food.

In a dose proportionality study involving multiple CMI doses, steady-state plasma concentrations (C_{ss}) and area-under-plasma-concentration-time curves (AUC) of CMI and CMI's major active metabolite, desmethylclomipramine (DMI), were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C_{ss} and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and CMI/DMI concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C_{ss} and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of CMI occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/ml to 154 ng/ml (mean, 92 ng/ml). After multiple daily doses of 150 mg of Anafranil, steady-state maximum plasma concentrations range from 94 ng/ml to 339 ng/ml (mean, 218 ng/ml) for CMI and from 134 ng/ml to 532 ng/ml (mean, 274 ng/ml) for DMI. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

Distribution: CMI distributes into cerebrospinal fluid (CSF) and brain and into breast milk. DMI also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of CMI is approximately 97%, principally to albumin, and is independent of CMI concentration. The interaction between CMI and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

Metabolism: CMI is extensively biotransformed to DMI and other metabolites and their glucuronide conjugates. DMI is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of CMI in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of CMI and DMI were only about 0.8-1.3% of the dose administered. CMI does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

Elimination: Evidence that the C_{ss} and AUC for CMI and DMI may increase disproportionately with increasing oral doses suggests that the metabolism of CMI and DMI may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, CMI and DMI may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of CMI ranges from 19 hours to 37 hours (mean, 32 hr) and that of DMI ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for CMI. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for CMI is approximately 2.5 and for DMI is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of CMI and DMI (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of Anafranil have not been determined.

Pharmacokinetic Interactions: Coadministration of haloperidol with CMI increases plasma concentrations of CMI. Coadministration of CMI with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated CMI better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of CMI were significantly higher in smokers than in nonsmokers.

INDICATIONS AND USAGE

Anafranil is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of Anafranil for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking CMI experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. CMI treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of Anafranil for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use Anafranil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Anafranil is contraindicated in patients with a history of hypersensitivity to Anafranil or other tricyclic antidepressants.

Anafranil should not be given in combination, or within 14 days of treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Anafranil is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS
Seizures

During premarket evaluation, seizure was identified as the most significant risk of Anafranil use.

The observed cumulative incidence of seizures among patients exposed to Anafranil at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates cited correct the crude rate (i.e., 0.7%, 25/3519) for the variable duration of exposure times among the patients who participated in the development program.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of CMI greater than 250 mg is limited, given that the plasma concentration of CMI may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Rare reports of fatalities in association with seizures have been recorded by foreign post-marketing surveillance systems over the 20 years of Anafranil's nondomestic marketing. In some of these cases, Anafranil had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions.

Caution should be used in administering Anafranil to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Physicians should discuss with patients the risk of taking Anafranil while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

PRECAUTIONS
General

Suicide: Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for Anafranil should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular Effects: Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking Anafranil in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with CMI in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

Psychosis, Confusion, And Other Neuropsychiatric Phenomena: Patients treated with Anafranil have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Anafranil. As with tricyclic antidepressants to which it is closely related, Anafranil may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

Mania/Hypomania: During premarketing testing of Anafranil in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to Anafranil.

Hepatic Changes: During premarketing testing, Anafranil was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

Hematologic Changes: Although no instances of severe hematologic toxicity were seen in the premarketing experience with Anafranil, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with Anafranil use. As is the case with tricyclic antidepressants to which Anafranil is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with Anafranil.

Central Nervous System: More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when Anafranil was used in combination with other drugs when Anafranil and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Sexual Dysfunction: The rate of sexual dysfunction in male patients with OCD who were treated with Anafranil in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

Weight Changes: In controlled studies of OCD, weight gain was reported in 18% of patients receiving Anafranil, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving Anafranil had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving Anafranil and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

Electroconvulsive Therapy: As with closely related tricyclic antidepressants, concurrent administration of Anafranil with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Surgery: Prior to elective surgery with general anesthetics, therapy with Anafranil should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

Use in Concomitant Illness: As with closely related tricyclic antidepressants, Anafranil should be used with caution in the following:

1. Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity.
2. Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug.
3. Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises.
4. Patients with significantly impaired renal function.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of Anafranil, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of Anafranil have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Anafranil:

1. The risk of seizure (see WARNINGS).
2. The relatively high incidence of sexual dysfunction among males (see PRECAUTIONS, Sexual Dysfunction).
3. Since Anafranil may impair the mental and/or physical abilities required for performance of complex tasks, and since Anafranil is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see WARNINGS).
4. Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since Anafranil may exaggerate their response to these drugs.
5. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
6. Patients should notify their physician if they are breast-feeding.

Drug Interactions

The risks of using Anafranil in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of Anafranil, caution is advised in using it concomitantly with other CNS-active drugs (see PRECAUTIONS, Information for Patients). Anafranil should not be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when Anafranil is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with CMI because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of CMI has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of either methylphenidate, cimetidine, or fluoxetine, and such an effect may be anticipated with CMI as well. Administration of CMI has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Pharmacokinetic Interactions).

Because Anafranil is highly bound to serum protein, the administration of Anafranil to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound Anafranil by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats given doses 20 times the maximum daily human dose. Three out of 235 treated rats had a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

Pregnancy Category C

No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetotoxic effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken Anafranil until delivery. Anafranil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Anafranil has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In a controlled clinical trial in children and adolescents (10-17 years of age), 46 outpatients received Anafranil for up to 8 weeks. In addition, 150 adolescent patients have received Anafranil in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14-17 years of age. While the adverse reaction profile in this age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with Anafranil may have on the growth and development of children.

The safety and effectiveness in children below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of Anafranil in children under the age of 10.

Use in Elderly

Anafranil has not been systematically studied in older patients; but 152 patients at least 60 years of age participating in U.S. clinical trials received Anafranil for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

ADVERSE REACTIONS
Commonly Observed

The most commonly observed adverse events associated with the use of Anafranil and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

Leading to Discontinuation of Treatment

Approximately 20% of 3616 patients who received Anafranil in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received Anafranil in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving Anafranil (N = 322) or placebo (N = 319) or children treated with Anafranil (N = 46) or placebo (N = 44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials
(Percentage of Patients Reporting)

Body System/ Adverse Event*	Adults		Children and Adolescents	
	Anafranil (N = 322)	Placebo (N = 319)	Anafranil (N = 46)	Placebo (N =
Nervous System				
Somnolence	54	16	46	1
Tremor	54	2	33	
Dizziness	54	14	41	1
Headache	52	41	28	3
Insomnia	25	15	11	

Anafranil® clomipramine hydrochloride

Body System/ Adverse Event*	Adults		Children and Adolescents	
	Anafranil (N=322)	Placebo (N=319)	Anafranil (N=46)	Placebo (N=44)
Libido change	21	3	—	—
Nervousness	18	2	4	2
Myoclonus	13	—	2	—
Increased appetite	11	2	—	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	2	—
Twitching	7	1	4	5
Impaired concentration	5	2	—	—
Depression	5	1	—	—
Hyperkinesia	4	1	2	—
Sleep disorder	4	—	9	5
Psychosomatic disorder	3	—	—	—
Yawning	3	—	—	—
Confusion	3	—	2	—
Speech disorder	3	—	—	—
Abnormal dreaming	3	—	—	2
Agitation	3	—	—	—
Migraine	3	—	—	—
Depersonalization	2	—	2	—
Irritability	2	2	2	—
Emotional lability	2	—	—	2
Panic reaction	1	—	2	—
Aggressive reaction	—	—	2	—
Paresis	—	—	2	—
Skin and Appendages				
Increased sweating	29	3	9	—
Rash	8	1	4	2
Pruritus	6	—	2	2
Dermatitis	2	—	—	2
Acne	2	2	—	5
Dry skin	2	—	—	5
Urticaria	1	—	—	—
Abnormal skin odor	—	—	2	—
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	—	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	—
Flatulence	6	3	—	—
Tooth disorder	5	—	—	—
Gastrointestinal disorder	2	—	—	—
Dysphagia	2	—	—	—
Esophagitis	1	—	—	—
Eructation	—	—	2	—
Ulcerative stomatitis	—	—	2	—
Body as a Whole				
Fatigue	39	18	36	9
Weight increase	18	1	2	—
Flushing	8	—	7	—
Hot flushes	5	—	2	—
Chest pain	4	4	7	—
Fever	4	—	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	—	—
Chills	2	1	—	—
Weight decrease	—	—	7	—
Otitis media	—	—	4	5
Asthenia	—	—	2	—
Halitosis	—	—	2	—
Cardiovascular System				
Postural hypotension	6	—	4	—
Palpitation	4	2	4	—
Tachycardia	4	—	2	—
Syncope	—	—	2	—
Respiratory System				
Pharyngitis	14	9	—	—
Rhinitis	12	10	7	5
Sinusitis	6	4	2	9
Coughing	6	6	4	5
Bronchospasm	2	—	7	2
Epistaxis	2	—	—	2
Dyspnea	—	—	2	—
Laryngitis	—	1	2	—
Urogenital System				
Male and Female Patients Combined				
Micturition disorder	14	2	4	—
Urinary tract infection	6	1	—	2
Micturition frequency	5	3	—	—
Urinary retention	2	—	7	—
Dysuria	2	2	—	—
Cystitis	2	—	—	—
Female Patients Only	(N=182)	(N=167)	(N=10)	(N=21)
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	—	—	—
Menstrual disorder	4	2	—	—
Vaginitis	2	—	—	—
Leukorrhea	2	—	—	—
Breast enlargement	2	—	—	—
Breast pain	1	—	—	—
Amenorrhea	1	—	—	—
Male Patients Only	(N=140)	(N=152)	(N=36)	(N=23)
Ejaculation failure	42	2	6	—
Impotence	20	3	—	—
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	—	4	—
Tinnitus	6	—	4	—
Abnormal lacrimation	3	—	—	—
Mydriasis	2	—	—	—
Conjunctivitis	1	—	—	—
Anisocoria	—	—	2	—
Blepharospasm	—	—	2	—
Ocular allergy	—	—	2	—
Vestibular disorder	—	—	2	2
Musculoskeletal				
Myalgia	13	9	—	—
Back pain	6	6	—	—
Arthralgia	3	5	—	—
Muscle weakness	1	—	2	—
Hemic and Lymphatic				
Purpura	3	—	—	—
Anemia	—	—	2	2
Metabolic and Nutritional				
Thirst	2	2	—	2

Other Events Observed During the Premarketing Evaluation of Anafranil

During clinical testing in the U.S., multiple doses of Anafranil were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to Anafranil who experienced an event of the type cited on at least one occasion while receiving Anafranil. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with Anafranil, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: Infrequent — general edema, increased susceptibility to infection, malaise. *Rare* — dependent edema, withdrawal syndrome.

Cardiovascular System: Infrequent — abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare* — aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System: Infrequent — abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare* — cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System: Infrequent — hypothyroidism. *Rare* — goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System: Infrequent — lymphadenopathy. *Rare* — leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder: Infrequent — dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare* — fat intolerance, glycosuria.

Musculoskeletal System: Infrequent — arthrosis. *Rare* — dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

Nervous System: Frequent — abnormal thinking, vertigo. *Infrequent* — abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. *Rare* — anticholinergic syndrome, aphasia, apraxia, catalepty, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

Respiratory System: Infrequent — bronchitis, hyperventilation, increased sputum, pneumonia. *Rare* — cyanosis, hemoptysis, hypoventilation, laryngismus.

Skin and Appendages: Infrequent — alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare* — chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

Special Senses: Infrequent — abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare* — blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

Urogenital System: Infrequent — endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, testis disorder, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare* — albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

DRUG ABUSE AND DEPENDENCE

Anafranil has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with Anafranil discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential Anafranil abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received Anafranil for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for Anafranil in foreign marketing, it is not possible to predict the extent to which Anafranil might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE

Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with Anafranil either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/mL. All 10 patients completely recovered. Among reports from other countries of Anafranil overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, CMI's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of Anafranil may not reflect the severity of poisoning: they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours before being observed until well after the cardiac status has returned to normal; relapse may occur after apparent recovery. The slow intravenous administration of physostigmine

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salicylate has been reported to reverse the cardiovascular and CNS anticholinergic manifestations of tricyclic overdosage; however, it should not be used routinely, since it may induce seizures and cholinergic crises and there is persisting debate about its net utility.

In the alert patient, the stomach should be emptied promptly by induced emesis followed by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Lavage should be continued for 24 hours or longer, depending on the apparent severity of intoxication. Normal or half-normal saline should be used to avoid water intoxication, especially in children. Instillation of activated charcoal slurry may help reduce absorption of CMI.

External stimulation should be minimized to reduce the tendency for convulsions, and anticonvulsants may be necessary. If MAO inhibitors have been taken recently, barbiturates should not be used. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, dopamine, or dobutamine by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of Anafranil in tissues.

DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials in 520 adults, and 91 children and adolescents with OCD. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both CMI and its active metabolite, DMI, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)

Treatment with Anafranil should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue Anafranil, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Anafranil after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

HOW SUPPLIED

Capsules 25 mg — Ivory/melon yellow (imprinted ANAFRANIL 25 mg)
  Bottles of 100 .... NDC 0083-0115-30
  Unit Dose (blister pack)
    Box of 100 (strips of 10) .... NDC 0083-0115-32
Capsules 50 mg — Ivory/aqua blue (imprinted ANAFRANIL 50 mg)
  Bottles of 100 .... NDC 0083-0116-30
  Unit Dose (blister pack)
    Box of 100 (strips of 10) .... NDC 0083-0116-32
Capsules 75 mg — Ivory/yellow (imprinted ANAFRANIL 75 mg)
  Bottles of 100 .... NDC 0083-0117-30
  Unit Dose (blister pack)
    Box of 100 (strips of 10) .... NDC 0083-0117-32

Do not store above 86°F (30°C). Protect from moisture.

Dispense in tight container (USP).

ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with Anafranil. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

C90-1

* Events reported by at least 1% of Anafranil patients are included

R_X

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Presidential Papers: 1990

Herbert Pardes, M.D.

Presidential Address:
Defending Humanistic Values

Herbert Pardes, M.D.

T he past year has seen a miracle in Eastern Europe. The iron curtain is disintegrating. With new and continuing victories in Czechoslovakia, Hungary, Rumania, Poland, and perhaps other countries in the foreseeable future, humanistic values are prevailing over half a century of oppression.

In this country, the resurgence of freedom in Europe has kindled new hopes. We have envisioned a shift of policies and resources away from old oppressors on another continent to the ranks of the needy here at home. To members of the helping professions, who have made it their business to keep the needy in sight, the previous and present Administrations seem to have lost sight of them. Of chief concern to us as physicians is the continuing erosion of our health care system. George Will, hardly a flaming liberal, described in a March issue of *Newsweek* the breakdown of our trauma care services and ended with the comment, "The President says, 'We have more will than wallet.' He has it backward" (1).

It was heartening recently when the House voted for a $24 billion cut in defense spending. How the budget evolves will determine whether, at long last, some of the wealth may be shared with domestic programs. The urgency of domestic needs is obvious. Without a doubt, the Administration bears substantial responsibility for the neglect that has allowed several major problem areas to reach the point of crisis. But elected officials alone are not to blame. They were elected by majorities of U.S. voters. Our citizens, according to

Tom Wicker, claim that they will support increased taxes for "a good and necessary purpose" (2). However, the experience of defeated liberal Democrats who were explicit about raising taxes for domestic programs proves otherwise.

If what comes out of the budget machinery in Washington is helpful to those in need, it will come none too soon. Our society's values have reached a low point. Instead of news about what is "good" or "necessary," front page stories for quite some time have been largely about greed: leveraged buyouts and junk bonds, pricey real estate deals, and Wall Street scandals. American teenagers, if they know how to read, read that. The United States has fallen behind several other countries in science education, as well as in several scientific disciplines (3). Our personnel needs in the health sciences and in the sciences in general are being met largely by people from other countries. For all its materialism, the country's productivity is slackening, while the problems facing the medical community—to whom most Americans must turn sooner or later—have become gargantuan. Hospitals, research institutes, and universities are starving. Americans spend millions on the lottery on the ephemeral chance that they might win, while in the lottery of health they are set up to lose.

Some may question whether politics on a national scale is uniquely relevant to APA. It certainly is, because APA and American psychiatrists care about inadequate reimbursement for psychiatric treatment, inadequate funding for research on psychiatric illness, inadequate resources for housing and for the homeless, and inadequate support for other mental health and social services. The country's political philosophy also matters at the state and local levels to any psychiatrist who cares about the fiscal disasters in states and cities and the drastic cuts in mental health services that go with them.

My message is that because humanistic values are

under siege in general in this country—and they are under massive assault in certain arenas that I would like to mention—I believe it is time for us as psychiatrists to make new efforts to defend these values.

PSYCHIATRY'S HUMANISTIC REWARDS

Humanistic values are at the very heart of our profession. The study of the mind, and the healing of the mental anguish that can rob people of the fulfillment of their humanity, is our life's work. To this work we bring both our own humanity and the force of modern science.

The rewards can be enormous. In the past decade, especially, we have been dazzled by advances in brain imaging, molecular genetics, psychopharmacology, and other fields of study that have revolutionized neuroscience. The most exciting aspect of these advances is what they promise for our capacity as physicians. Because of this panoply of research—encompassing high-tech findings about the brain, evaluation of the psychotherapies, linkage studies, epidemiology and the refinement of diagnostic criteria, the discovery of effective medications, and the development of effective rehabilitation—we can see and begin to deliver new kinds of relief for mental suffering. Few of us would have dreamed that these advances were possible in the days when we entered the field. It has been very moving to find that our progress is understood and appreciated by our patients, their families, and our other friends in the citizens' movement, who are now devoting their own considerable vitality and talents to the fight against mental illness.

But today there are forces gathering that could jeopardize this progress and the humanistic values that it affirms, and we are going to have to fight to preserve it. As psychiatrists we share values and objectives that I believe can make us—together with our allies in the citizens' movement—a powerful, positive force.

PSYCHIATRY'S VALUES AND OBJECTIVES

1. First and foremost, we care about our patients. We are physicians, and we are the ones who chose to treat mental anguish.

2. Because we care, we believe in accessible health care for everyone. Reimbursement for health care would do much to relieve the misery not only of patients, but also of doctors and nurses who find themselves in the excruciating position of not being able to take care of people who need it but cannot pay. Comprehensive health care coverage would also help prevent fiscal calamity for our health care institutions.

3. We must have equitable reimbursement for psychiatric treatment. We do not expect unlimited coverage—some copayments and other limits are necessary throughout medicine—but let all medical specialties share them. We believe in, and will work until we get,

coverage on a par with other kinds of health care. Although we won a victory for our patients in eliminating Medicare limits on treatment, after working to achieve it for over 20 years, the legislative journey on the road to nondiscriminatory coverage has not ended. Now we must work toward equal patient copayments for all medical treatment.

4. We value both excellence and progress in the enterprises that serve humanity, specifically health care delivery and biomedical and behavioral research.

5. To ensure such excellence and progress, we must have a strong national program of research and development. We have a serious problem when this country, which in the past put 2.7% of the gross national product into civilian research and development, is now down to about 1.7%, while four other countries in the same 20- to 30-year period have gone in the opposite direction. I do not think any of us wants the United States to be second-class in biomedical research to Japan and Germany.

Specifically, our hospitals and other health care institutions, and our sciences, need major attention. With respect to psychiatry, it is vital to support a broad spectrum of both research and methods of patient care. The quality of life of psychiatric patients depends on continuing progress in neurobiology, biotechnology, epidemiology, psychosocial treatments, and new approaches to rehabilitation. And many approaches to treatment are essential to address a multiplicity of needs—pharmacotherapy, the psychotherapies, the behavior therapies, ECT, intervention in family dynamics, and multiple group family therapies. We must ensure that all are available.

6. We must work, therefore, for increased support. The potential of brain imaging, molecular genetics, neurobiology, and immunology research is phenomenal. We must not let this potential go unrealized. In genetics, to give only one example, in the past 5 to 10 years, linkage studies and other techniques have located genes for cystic fibrosis, muscular dystrophy, familial Alzheimer's disease, Huntington's disease, and manic-depressive disease.

Now there are new waves of scientific excitement. By selectively replacing a normal gene in a mouse with a gene known to create abnormalities, we can observe the specific effect of changing one gene. A beautiful, recent study in the journal *Nature* reported that introducing a gene for a growth hormone defect produces midget mice (4). A scientific development of this magnitude could help clarify how many different diseases develop. If we can gain access to a gene that causes manic-depressive illness or familial Alzheimer's disease, we may be able to determine in mice which pathways are selectively affected. Such findings would provide a clue to how the pathogenic gene sets off the disease cascade in the human.

In *Science*, another exciting advance was recently reported: for the first time, neurons from the cerebral cortex have been grown in the laboratory (5). Clones of this cell line will be available to other neuroscientists

for genetic studies, biochemical studies, and transplantation studies. The implications for psychiatry could be substantial. The day may actually be in sight when we can graft brain tissue, delivering needed cells and hormones to brain regions where tissue has been destroyed by illness or injury, and finally offer hope to patients with schizophrenia, Alzheimer's disease, Parkinson's disease, drug addiction, and many other disorders. But to do so we need the scientists, the laboratories, the equipment, and the support for young, mid-career, and senior scientists.

I was heartened recently, while testifying before the Senate Appropriations Committee, to find that Senator Hollings from South Carolina is prepared to lead the charge for more support for research. Congresswoman Barbara Boxer has argued for the same increase for the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) that APA suggested. This followed APA's success in convincing the Ad Hoc Group for Medical Research Funding, a coalition of more than 140 medical and scientific societies and voluntary health organizations dedicated to the funding of biomedical research, to support our ADAMHA alternative budget. Congresswoman Boxer wrote to Leon Panetta of the House Budget Committee requesting an increase of 40% in ADAMHA research and an increase of 23%–24% for research at the National Institutes of Health (NIH). These increases would bring ADAMHA's research budget to $1.2 billion and NIH's to about $9.2 billion. These are numbers that are more responsive to the need. It is one thing to get the standard 4% or 5% increase each year. But when a private business firm finds out that it has a hot prospect, it does not increase the budget 4% or 5%, it increases the budget 50% or 100%. The hot prospects are there in research now, and we want the budget increase to happen now.

7. We believe in assigning high priority nationally to basic human needs. The most grossly neglected of these needs is conspicuous in the national disgrace of homelessness. It is an outrage that people live in the gutters of this country. It was shocking to see the recent report that a black man in Harlem has a shorter life expectancy than a man in Bangladesh (6). It seems impossible that any Americans could allow their fellow citizens to endure such deprivation and squalor. But if there are Americans who choose to avert their eyes from people in need, psychiatrists must be prepared to confront these problems directly. We do not want to hear our leaders *talk* about housing. We want to see them *do* something about housing.

8. Also among the "good and necessary purposes" that we believe warrant public support are programs to assure that people from all walks of life can become doctors, scientists, and academic leaders. To begin at the beginning, we place value on the lives of young people who are economically disadvantaged. We believe in extending a strong lifeline to them, with programs to connect inner city youngsters to creative and constructive possibilities—schools, jobs, family lives.

We are not willing to abandon them to the bleak legacy of drugs and violence. There is evidence that young people who are productively involved in school do not fall prey to drugs (7). It can hardly surprise us that if the country ignores disadvantaged youngsters and offers them nothing worth doing and no tangible constructive goals, they succumb to the pressures of their dismal lives.

9. On principle, as well as for practical necessity, we support the work ethic. Rededication to the value of work is surely indispensable to turning this country around. What can we expect from a society that fosters a 9 to 5 mentality, with a rush to the bars and the television screens at "quitting time"?

10. For those who enter the helping professions, idealism and altruism should not cost so much. We must try to balance the grotesque disparity of the reward system, so that becoming a scientist, a nurse, an X-ray technician, a physician, a psychologist, a social worker, a phlebotomist, or a teacher does not mean a future of barely making ends meet, while young lawyers and Wall Street traders make salaries two, three, and four times greater. Columbia University's President Michael Sovern has remarked that his son commanded a higher starting salary at a prestigious law firm than Sovern did when he became dean of the law school.

These are only a few examples of our concerns. APA has taken official positions to work toward an end to racism in this country and an end to homophobia. It is working on a statement about apartheid. There are other social wrongs that we, as individual citizens, want to put right. But as we persevere in those private efforts, it is a privilege to know that we are practicing a profession that is itself devoted to humanistic causes. This distinguishes us from many in a culture where the goal of life is, in a popular phrase, "having it all."

PSYCHIATRY IN THE 1990s

Psychiatry in 1990 is at the height of its powers. We have had a spectacular decade, getting more than back up to speed in the 1980s after a trying time in the 1970s. In the middle 1970s, with the community mental health center movement under attack for not taking care of the seriously mentally ill and psychodynamic psychiatry under fire for not solving the problems of the world, we worried with good cause about the related drop in the numbers of applicants to psychiatric residencies.

The 1980s were another story. Neuroscience and biotechnology blew away old barriers to knowledge. Nobel Prizes and Lasker Awards, and now Lieber Awards, testify to the surge of groundbreaking research. Some of this research revealed ground shared by biological and psychological approaches to the human mind. Psychiatry entered the mainstream of medicine once and for all. Our student applicants grew in number. The press we get now includes the brilliant

article by Erica Goode in a recent issue of *U.S. News and World Report* (8). It is titled "Beating Depression: New Treatments Bring Success," and is subtitled, in the table of contents, "Psychiatry's Big Success Story." There has been quite a change in 15 years.

As the 1990s begin, we face an array of possibilities and an array of problems once again. I would like to call attention to what I believe may prove to be the single most important piece of good news for our profession. I also want to focus briefly on a problem that could be very bad news unless we rally the humanistic values from which psychiatry draws its greatest strength.

THE GOOD NEWS

The good news is that we have made friends with the families of our patients, and the constituency for the mentally ill has at long last not only begun to take shape, but also to grow by leaps and bounds. Citizens' groups, including the National Alliance for the Mentally Ill (NAMI), the National Mental Health Association, the National Depressive and Manic Depressive Association, the Anxiety Disorders Association of America (formerly the Phobia Society), the National Alliance for Research in Schizophrenia and Depression (NARSAD), and others, are expanding at a phenomenal rate. NAMI, which did not exist before the 1980s, enlarged its membership to close to 100,000 in less than 7 to 10 years. The American Mental Health Fund has mounted a brilliant national advertising campaign to educate the public about mental illness. Local associations of NAMI, the National Mental Health Association, and other organizations are working with local groups of mental health professionals to advocate for our patients and for mental health programs. In the past 2 years, citizens worked together with us to secure the largest boosts in support ever made for NIMH, and this success fuels the effort this year to do it again.

I would like to single out NARSAD as a spectacular example of what the citizens' groups have achieved on behalf of both the mentally ill and our profession's efforts to help them. This organization was formed by the citizens' groups themselves and received some financial assistance from APA to get started. NARSAD's mandate is to raise support in the private sector for research in the major mental illnesses. In its first year in action, 1987, NARSAD hoped to give $50,000 in awards. Whether the organization could even get going, with that sum, was touch and go. Three years later, on March 29, 1990, Connie Lieber, NARSAD's extraordinary president, who was honored at APA's 1990 annual meeting, announced that NARSAD is giving $3.6 million in awards this year to 60 young investigators and 11 established investigators. Among NARSAD's efforts is the Lieber Award, now the leading research prize in psychiatry. The 71 new grants, added to the number made in previous years, bring the total number of NARSAD awards and commendations

to over 135, or nearly $7 million in 3½ years. Connie Lieber likes to see things move and grow fast. She and the others at NARSAD are pulling it off: the early goal of $50,000 for 1 year has been multiplied 72-fold.

If we consider that between 15% and 19% of the American people have a psychiatric illness at any one time, and if even one family member is concerned about each patient, we are talking about a potential army of 30% to 38% of the American population, which means something like 70 to 90 million people. That is a lot of votes. As the campaign against stigma makes further inroads, the number of these individuals who can be expected to go into action on behalf of the mental health enterprise will continue to grow. This will be a key factor in sustaining the growth and excitement in psychiatry in the decade ahead. Our citizen allies will help us prevail in spite of a social climate that may be more attuned to the people on magazine covers and talk shows than it is to people in need.

THE BAD NEWS

The bad news is that a number of ideological extremists are interfering with medical treatment and medical progress in order to impose their own moral positions on the rest of the country. Some demean and discriminate against patients with illnesses that arouse their moral wrath, notably AIDS and substance abuse disorders. It is our conviction that a patient's right to treatment has nothing to do with the nature of the illness. APA has taken policy positions asserting this view. APA has worked and will continue to work to defend patients against discrimination of this kind.

There are also groups whose members are primed to interfere directly in other people's lives, even at the expense of those lives. One group consists of those who oppose a woman's right to choose an abortion. There are many who find abortion personally unacceptable; this is their right and their choice. However, last year a lawsuit by anti-abortionists actually interfered with the recommendation *by doctors* to abort a fetus to try to save a comatose woman's life. Her anguished husband, who was not prepared to watch his wife and the mother of their other child die for the sake of a fetus, was forced to go to court to fight these total strangers. This astounding and very nearly tragic intrusion is only the tip of the iceberg if the opponents of a woman's right to choose are allowed to dictate their terms to this country.

In addition, the moratorium on federal funding for research using fetal tissue, imposed by the Reagan Administration pending recommendations by panels at NIH, remains in force *despite* recommendations by the panels that it be lifted. The study of fetal tissue is one of the most promising research approaches available today, notably in areas such as genetic illness, treatment of Parkinson's disease and Alzheimer's disease, and the neuropathology of maternally transmitted AIDS. But both the Reagan and Bush Presidencies have

disregarded scientific advice at the highest levels in favor of vocal pressure groups that have a "moral" problem with the use of fetal tissue by medical scientists, on the alarmist premise that it will encourage abortion. In addition, the State of Pennsylvania has banned all research of this kind.

It is a fundamental tenet in this country to respect the right of individuals to hold whatever moral beliefs they choose. But it is also a fundamental tenet that no group may force its own moral system on others.

I must also call attention to another group, a large group—although very few people are aware of its size and strength—that is on its way to imposing its own code of morality on an entire country, however many people's hopes for health or for life are sacrificed in the process.

In my year as President, I have placed a major focus on the animal rights movement because only a tiny fraction of the people in this country are aware of the grim truth about its moral premise, how much its power has grown, or the kind of tactics it uses. I realize that this is a highly sensitive issue and that a number of our members have serious reservations about medical research using animals. Most of us have humanitarian concern for animals, whatever the setting. In a perfect world, perhaps we would not need to use them at all in medical science. But we do still need them. Only animals can teach us certain aspects of the etiology of disease or the value of new treatments or surgical procedures. A new drug should not pass directly from the test tube to your child.

In a public service announcement recently produced by former Surgeon General C. Everett Koop, he stated that when he was born, there was no vaccine for polio, there were no antibiotics, and there was no way of treating diabetes or heart disease. He further pointed out that the life expectancy in the United States then was 52 years. Today, all of the treatments mentioned have been produced through research using animals, and our life expectancy now is 72 years. Had animal activists been successful when Koop was born, we would have no effective measures against any of these illnesses, and many of us would live lives shorter by as much as 20 years. There are, of course, a number of terrible diseases for which we still do not have adequate treatment.

The problem is that human life and human health are regarded by animal activist leaders as no more important than animal life. This movement's guiding principle was spelled out as follows by one of its leaders: "There is no rational basis for separating out the human animal. A rat is a pig is a dog is a boy. They're all mammals" (9). The movement's leadership regards even painless research as "fascism" and "supremacism." It regards *any* use of animals for human purposes as "speciesism," and declares that animal rights are *as compelling* as equal rights for blacks and equal rights for women. Activist leaders have said that their mandate to end animal research now is *as urgent* as the

mandate was in World War II to stop the killing of Jews by Nazi Germany.

Most supporters of the animal rights movement believe they are promoting only the humane treatment of animals. Most of them very likely do not know that several activist leaders often compare animal research laboratories with Nazi concentration camps. Most almost certainly do not view themselves as sacrificing the health or life of people. But by supporting these organizations, they are actively working against the health or life of many fellow citizens, including family and friends, whether they see it that way or not.

Most of the movement's supporters are also very likely unaware of the subtlety and questionable honesty of some of its tactics. The movement's sophisticated and well-financed organizers (their collective treasury is some $50 to $200 million) have inspired massive letter-writing campaigns to elected officials, in large part by painting a grotesquely distorted picture of medical science and medical scientists. They have brilliantly manipulated the media, and they are making calculated efforts to intimidate, demoralize, and silence all opposition. Along with horrible insults, they have made death threats to researchers, laboratory animal veterinarians, and their children. They have telephoned scientists at night in their homes, dropping nightmarish hints about what they might do next.

Recently a courageous reporter published an article in *The Washingtonian* magazine about some of the animal activist activities (10). One activist group has now confronted her with a $3 million libel suit. The reporter, Katie McCabe, who cannot afford more than one libel suit at a time, has canceled all of her speaking engagements. Activists also sue individual scientists. And they break into laboratories, they destroy data, they smash computers, they smash microscopes, they set fires. They release infected laboratory animals. Mice being used in AIDS research at Stanford University are now kept under 24-hour guard. The Animal Liberation Front—ostensibly the radical arm of the movement, but an arm that commands support from several other ostensibly nonviolent groups—is listed by the FBI as one of the 10 most dangerous terrorist organizations in the United States.

Psychiatry and biobehavioral science are primary targets of the animal rights movement. Psychiatry has had enemies before, but never before have we been up against people who are prepared to say on the radio, of a medical researcher, "The sooner he is killed, the better" (BBC radio interview). In England, police believe that it was the Animal Liberation Front that bombed and destroyed part of a Bristol University administration building. This past April, an animal activist in Connecticut was convicted on federal charges of attempted murder, possession of explosives, and bomb manufacturing after planting a remote-controlled pipe bomb near the parking space of the chairman of U.S. Surgical, a corporation that supplies surgical instruments. The activist entered a plea of no contest to the charges.

On behalf of our patients, we must oppose the animal rights movement, and we must oppose it now. Of course, we want animals properly cared for and used as sparingly and humanely as possible. Yes, there may have been a time when animal rights activists had some legitimate concerns about the manner in which animal research was carried out in some institutions, and there may have been researchers who did not conform to the many scrupulous standards intended to protect animals. These individuals must be reprimanded appropriately. But if such abuses did occur in the past, they are highly unlikely to do so in the future. The many current regulatory mechanisms include institutional animal care and use committees, which have the same kind of formal review procedures as institutional review boards for research on humans. In essence, research using animals must be as rigorously justified as research using human subjects.

Any individual who would abuse animals in a medical setting is a person with inadequate professional and ethical standards. Such a person is far from typical of the medical research community, and to suggest otherwise is misinformation. We must counteract it with real information. The vast majority of researchers trying to find cures for such diseases as cancer and schizophrenia and manic-depressive illness are dedicated people who persist in trying to advance our ability to help the sick. And they are doing it on modest salaries, with constrained resources, against increasing bureaucracy. Now they are hearing themselves compared to Nazis and incurring physical risks to themselves as well as the risk of having years of their work demolished by individuals who destroy or steal their animals, data, and equipment.

I am heartened by the fact that Congressman Vin Weber of Minnesota has launched a proresearch Congressional group called the Animal Welfare Caucus and that Congressman Henry A. Waxman of California, Senator Howell T. Heflin of Alabama, Congressman Charles W. Stenholm of Texas, and others are starting to assert themselves as leaders to defend and support research using animals. We must support these courageous elected officials. We must also write letters to our other representatives and help them understand the differences between compassion and extremism, help them remember that human lives are at stake. But we must do more than that. It is urgent that clinicians dedicate themselves individually to helping laypersons understand the need for animal studies in medical research. We hear animal activists say that not only is psychiatric illness not real illness, but that even if it were, it would be immoral to use animals to study the mechanisms of *any* human illness. We must tell people we know, at every opportunity, the other side of this story.

A nation's direction can come from its elected officials. But when the officials waffle about the most pressing ethical matters, presumably because they care more about being reelected, it is time for action by groups of people who are willing to work for the values in which they believe. As physicians and psychiatrists, we are among the most highly educated people in the United States. It is appropriate for us to demonstrate ethical leadership in a country so demoralized that it waits in front of the television set to be told what to care about next. It is appropriate that we speak out on behalf of the sick and the poor in a country that has lost sight of the needs of real people but eagerly follows the headlines about a new casino that has to bring in $1 million a day to break even, and does. It is appropriate for us to defend human beings in a country where policy makers are being pressured by people who state that the lives of rats, pigs, and dogs are equal to the lives of boys.

SUSTAINING THE EFFORT

As Dr. Elissa Benedek takes over as President, I am happy to tell her that our profession and our association are in good shape and in good hands. We have made great progress. We can take pride in the fact that prejudice against psychiatry and psychiatric patients is fading. Psychiatry works, psychiatry is respected for it, and we can hold our heads high.

Perhaps best of all, we can at last begin to see a decline in stigma. We will not rest until stigma is a thing of the past, and we will make that happen by educating the American public. We must all spread the word that we can relieve most depressions and most anxiety disorders, and we can offer new relief to people with obsessive-compulsive disorders. We have new medications for people with schizophrenia and new behavioral and biological treatments for many other psychiatric conditions.

We still have serious difficulties as the 1990s begin. Obtaining money to build the mental health enterprise is an ongoing struggle. Researchers are having increasing trouble getting support. Managed care presses harder and harder on our clinicians. The cost of mental health care has risen. This fact reflects, in part, a success story; the rise has occurred to some extent because people who did not come to us for help before now recognize that we can help them and are seeking us out. But increasing demand poses a serious problem that we have yet to solve.

We also still have a long way to go to help many other patients with schizophrenia, with borderline conditions, with illnesses for which the course is unknown or totally unpredictable, with illnesses for which our current treatments are limited. These patients and their families are in deep distress. Our researchers are working hard on these problems. This is a message that we must spread, both to give hope to suffering people and because broader public understanding is critical to efforts at obtaining reasonable reimbursements, which we need in order for our treatments to be available and accessible.

CONCLUSIONS

Psychiatry has been called the art of the possible. Whether we as individual members of our discipline regard our work principally as an art, principally as a science, or as an unquantifiable blend of both, I think we would all agree that more is possible now than ever before.

We must not allow anything to slow our momentum.

I called my theme for this year "The Research Alliance: Road to Clinical Excellence." I believe that it is because of a spirit of alliance—collective and collaborative efforts by researchers, clinicians, and citizens—that so much has been accomplished. It is thrilling to see researchers battle the complexities of psychiatric disease and win more and more battles. It is thrilling to foresee that these discoveries will ultimately enable us to help many more people. And it is thrilling that our profession and the people we are trying to serve are now comrades. In my 30 years in this field, I have had, along with many of you, the privilege and good fortune to see history in the making. It makes me happy today to know that, whatever President Bush may have by way of either will or wallet, *we* have the will, and we are working on the wallet all the time.

Yes, there are problems ahead. But we are ready to tackle them. I ask you all, members and friends of this association, to join in making the 1990s a decade of solid progress on behalf of our patients. I ask you as allies to fight policies that make proper mental health care unaffordable to people in need. We have had to fight before, to fight virtually every step of the way. We have fought stereotypes, prejudices, misconceptions, fear, and self-interest. We have fought for recognition as a medical discipline and won. We have fought for a society that views mental illness with compassion: we are still carrying on this fight, and we have begun to see that we will prevail. And we have fought for a fair share of public support for our research and for our treatment programs. This ongoing campaign is one for which, I am glad to say, we are both seasoned and still fresh. Being seasoned comes from gaining considerable ground. We are still fresh because we have to be: there

are plenty of hurdles left on this front. But as an alliance, clinicians, researchers, patients, and families *do* have the strength to oppose abuses of the concept of managed care and the imposition of impossible limits. We can and *will* ensure that our patients are not cheated in the name of controlling health care delivery costs. We will support leaders who regard human rights as more compelling than animal rights. We will support with our votes leaders who are concerned about the mentally ill and about mental health programs, and we will work to defeat leaders who are not.

Together, now more than ever, we are a force to be reckoned with. What we all want is a country where psychiatric illness is no longer met with fear and prejudice but with compassion and effective help. Together, we are going to go out and see to it that the people who need that compassion, who need effective help, and who need caring and knowledgeable professionals have their needs answered.

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Response to the Presidential Address:
Our Children: Our Future

Elissa P. Benedek, M.D.

I t is a great personal and professional honor to have been elected the 119th President of APA and, now, to have the opportunity to respond to Dr. Herbert Pardes' provocative, inspiring, and challenging Presidential address. Think of it, in 1994 our organization will be 150 years old, yet it remains in excellent health. It is also a personal and professional honor to be here, surrounded by family, friends, and colleagues who have known and supported me from childhood through adolescence and maturity with love, understanding, and encouragement. I thank all of you most sincerely.

In preparation for the challenging year that lies ahead, I have used a coping technique that has worked before—to take a moment to look back before moving forward. So I have read and reread the Presidential addresses and responses of my predecessors. Learning many of their hopes, fears, and dreams has been educational and has put into better perspective the year and challenges that are now before me. Parenthetically, I was amused on occasion by the grandiosity of their ideas. For example, one past president suggested that organized psychiatry should "take a more active and responsible part in the effort for elimination of the war psychosis" and suggested that when the history of psychiatry in the twentieth century came to be written, he hoped that it might be recorded that APA was largely responsible for the elimination of the great international psychosis—war (1).

Although we are seeing great progress in that direction—witness the dramatic changes in Eastern Europe, the Soviet Union, and super power relations—it would be difficult to attribute this to organized psychiatry. This should, perhaps, serve to remind us that while lofty goals are desirable and often attainable, we should not overestimate our capabilities or fantasize our mandate. This is not to suggest that global events are irrelevant to psychiatry. On the contrary, conferring with colleagues in the Eastern Bloc, sharing

knowledge and skills, and eliminating political abuse continues to be an important focus. Moreover, is it too much to hope that reduced spending for defense may result in support for vital domestic programs? Although there is some appropriation for basic clinical research, unless adequate funding is provided for the care of our youth, especially the poor and unemployed, the backdrop against which mental illness and emotional disorders develop will remain unchanged.

When I assumed the position of President-Elect, my first official address was at the Institute on Hospital and Community Psychiatry in Philadelphia, home of Benjamin Rush, father of psychiatry, and there I called upon his spirit and guidance. In the first paragraph of his book *Medical Inquiries and Observations Upon the Diseases of the Mind* (2), Dr. Rush prayed for guidance. He said,

> I feel as though I am about to tread on consecrated ground. I'm aware of the difficulty and importance of it and most humbly implore that being whose government extends to the thoughts of all its creatures to so direct mine in this arduous undertaking that nothing harmful to my fellow citizens may fall from my pen and that this work may be a means of lessening the proportion of some of the greatest evils of human life. (2, p. 9)

That prayer, written in 1812, expresses my sentiments for the strength and wisdom to lead our organization in a direction that lessens the proportion of evil and illness in human life.

Dr. Pardes has addressed us with great enthusiasm in regard to "The Research Alliance: Road to Clinical Excellence" (3), but that road will not be traveled unless we understand current research and are able to translate it clinically, humanely, and ethically. Some years ago, satirist Tom Lehrer, commenting on the ease with which a renowned German rocket scientist could shift, after the war, to the American program, observed in the song, "That Was the Year That Was," "Once the rockets are up who cares where they come down. That's not my department, says Wernher von Braun." It is the researcher's job to send up the rockets, but it is the job of all of us to see that they come down in the right place, that the fruits of research are improved clinical practice and quality programs.

Research has opened up new vistas in the exploration of behavior in and out of control. While research

findings often reflect a disconcerting lack of precision, and uncertainty may exist as to their specific applicability and effectiveness, all of us recognize that we must incorporate basic research findings into our clinical practice. Among the general population, however, I fear that it is only the rare individual who is even remotely concerned about basic or clinical research, let alone the lack of research support for programs designed to understand and combat poverty and deprivation and other social symptoms of mental illness such as homelessness, loss of meaningful relationships, and unemployment.

As I read through the addresses of past Presidents, I noted certain recurring themes: respect for research; concern about changing economics; concern for the compassionate, humanitarian, and ethical care of patients; and a need for creativity and personal dedication in challenging times. No one can argue with the timelessness of these kinds of themes, and they merit repetition. Yet, as I searched for a theme for this year I was drawn to my own training and interests. For many years, I have been interested and specially trained in two areas: child psychiatry and understanding violence, including treating the violent patient and victims of violence. If you think that these two areas, violence and child psychiatry, are not likely to interface, let me give you just one clinical example.

Recently, I was asked to see "Missy," a 10-year-old child, and give an opinion as to whether she still merited government Supplemental Security Income payments. I had seen her 5 years earlier and had recommended that she receive these funds. In addition, I had urged that she begin a course of psychotherapy. She was a child of poverty, a child of the ghetto, and had more than her share of burdens to carry. Missy's mother, who was an abuser of a number of substances, including alcohol and heroin, had neglected and abused her. Her father was also a heroin addict. She and her two siblings had lived with their parents until the state terminated parental rights because of abuse and neglect, particularly the filth in which they lived and the child beatings that were part of their daily lives.

Missy was placed with her grandmother and stepgrandfather and once again came to the attention of the state when there were proved charges of sexual abuse. The stepgrandfather, who had paranoid schizophrenia, had severely and repeatedly abused both Missy and her younger sibling, threatening to kill them if they ever disclosed this. But they did tell. After a protracted court battle, the siblings were placed first with other family members and finally with an aunt who was single, was unable to have children, and who desperately wanted a child.

Recently, 5 years after this placement, Missy once again appeared for an evaluation in my office with her aunt. From the record and from her aunt, I learned that Missy was in a special education program and, although a "slow learner," was doing reasonably well in her fourth-grade placement. However, according to

routine IQ testing she was too intelligent for that program, and all the special help she had been getting was to be terminated because she did not meet the state guidelines for retardation. Moreover, important therapy had never been initiated. Missy's aunt was more concerned with Missy's younger sister who, unlike Missy, was rebellious and quarrelsome. Missy still longed to go back to her parents. When asked to draw a picture of a family she drew her mother, who by this time was incarcerated in prison, her father, who had just been released from prison, her older brother, who was now living with another relative, her sister, and herself, smiling and happy, at a family Thanksgiving dinner that was and would remain pure fantasy. The real Missy is one of the saddest children I have ever seen.

What's to become of Missy? How will she grow up? Can she escape a cycle of abuse and neglect? Can we help her? Can we help her sister or her aunt? I do not know, but I am certainly going to try. Fitting Missy and her mental and emotional symptoms into the current *DSM* will be a challenge; developing a treatment plan and ensuring compliance will be even more of a challenge. I am sure most of my colleagues would agree that facilitating desperately needed treatment takes precedence over any consideration of remuneration. It is not yet clear to me, in fact, whether current Medicaid guidelines contemplate this situation. Yet, Missy is one of our children, part of our future.

In clinical activities such as these, I will follow the road map that Dr. Pardes outlines, applying new basic and clinical research in the treatment of children. I have told you about Missy because her case is illustrative of the all too common interaction of two areas— children and violence—that might seem to be entirely separate and apart and because her circumstances underscore the destructive psychological consequences that mental illness and emotional disorder in parents and caretakers often bring about.

When I talk about parents and children, I do so in the most traditional sense. Still, for one thought I might make an exception. All of us were once somebody's child, and many of us are now, or will be, somebody's parent. Our parenthood, however, extends beyond that. We will serve as mentors, teachers, and role models, fulfilling an important part of the parenting role for future generations of medical students, residents, and colleagues. Indeed, the future of our profession will be in their hands, so it is incumbent upon us to take very seriously this aspect of our parental obligation.

This seems a remarkably appropriate time to embark upon the theme "Our Children: Our Future." Historian Michael Katz wrote, "throughout the country, by the 1890's, children had captured the energy and attention of social reformers with an intensity never matched in other periods in American history" (4). What better time than the 1990s to refocus American public and political attention on children. Indeed, there appears to be renewed interest in children's issues

in our society, perhaps to a greater extent than at any time in the past century. Writing about the 1890s, Katz went on to say, "Almost overnight it seemed, children became the symbol of a resurgent, reformed spirit, the magnet that pulled together a diverse collection of causes and their champions into a new, loose, informal but effective coalition."

In the 1890s, a number of factors contributed to the emergence of a national spotlight focused on children. Some of those exist today, and others are somewhat different. The demographics, for instance, are different. Minors constituted almost half the population of the United States in 1890 (46%), barely a smaller percentage than the adult, nonaged population (50%), and the elderly comprised about 4% (5). Today, with the declining birth rate, coupled with the fact that more Americans are living longer, minors constitute only about one-quarter of the total population, and the proportion is likely to continue to diminish. Indeed, one could argue that children are a scarce national resource, one that is destined to become even more scarce. In addition, about 74 million people, more than one-third of the population, are "baby boomers," many of whom are now parents. They constitute close to half of the voting-age population, and most of them are working parents, that is, either single-parent or two-parent working families. For the first time there is a large middle-class population that is advocating for children out of its own self-interest.

These working parents are advocating a series of policies, primarily governmental, related to improving the balance between work and family life and which would support, financially and otherwise, child rearing for people in the labor force. With more than half of all wives working from the time their child is 1 year old, pressure is increasing to lessen the burden of these families through child-family policies such as federal subsidies for child care, job-protected leaves from work, paid time off to care for an ill child at home, day care, and maternity and paternity leaves. This pressure will not disappear. The national public debate, for instance, is no longer whether to subsidize child care but how to subsidize it, through what strategies, and for which parents and which children.

Significant changes in family structure in the latter half of the nineteenth century contributed to a changed perspective with respect to children, and the essence of it remains today. Industrialization had transformed America in the 1890s. As the family farm gave way to the factory, more men worked outside of the homestead, and middle-class wives, no longer performing farm chores, were able to stay home and concentrate on rearing their children. First in middle-class families, children began to be valued in their own right rather than as an economic resource, that is, a source of inexpensive farm labor for their families. With no farm to work, the economically "worthless" child at the close of the nineteenth century became the "priceless" child of the twentieth century, and societal concern shifted to children's health, welfare, and education.

The death of a young child was now viewed as a tragedy rather than with resignation, as it had been in the past.

Social goals now included the preservation of the child's life, health, and happiness. Infant and child mortality rates became tests by which the success of new child reforms could be measured. In addition, the changing view of the value of children was affected then, just as it is today, by growing recognition of the need for a more skilled and better educated labor force. Employers and middle-class parents joined together in a new appreciation of the value of education in developing "higher-quality" children who would mature into higher-quality adult workers. Society began to recognize that the well-being of children was, in fact, the key to the development of a responsible adult citizenry. Thus, a broad-based coalition of families, industrialists, political reformers, and social reformers developed an agenda for children's policy that included a campaign against child labor, advocacy for introduction of mothers' pensions, and reformation of the juvenile justice system and establishment of juvenile courts.

This new agenda also embodied educational reform, including the expansion of compulsory education; the expansion of preschool, kindergarten, and after-school programs as a device for meeting the language, academic, and social deficits of poor and immigrant children; and public health legislation to reduce infant mortality. Also contained in this comprehensive agenda for children's policy was a campaign against poor housing and the creation of new public and private institutions to carry out research and create new systems of service delivery for children. In short, the last decade of the nineteenth century saw the emergence of an agenda developed by a broad-based coalition that reflected both the importance of children in our society and the need for social programs that would focus on their best interests. Impact was inevitable—witness such events as the first White House Conference for Children in 1909 and the establishment of child guidance clinics and juvenile courts.

Now, in 1990, the public spotlight has once again focused on a children's agenda. Both major political parties apparently share the belief that children's issues are of high priority to many, if not most, Americans. As in the last century, different political constituencies have coalesced around these children's issues. Once again, a great many families, industrial leaders, labor leaders, social scientists, and politicians agree that we are not adequately protecting our nation's most precious resource, that we are not safeguarding our future.

This kind of concentration by a new amalgamation of interest groups results, as one would expect, from a number of conditions, any one of which would be difficult to ignore. Some of these should be noted here.

1. Continued low fertility rates, leading to a declining number of youth entering the labor force,

2. Declining school performance despite increas-

ing complexity of technology and fierce worldwide competition,

3. Dramatically changed roles of women as more mothers, both wives and single parents, enter and remain in the work force despite pregnancy, child birth, and child rearing and the concomitant scarcity of adequate child care,

4. Lack of success in educating and training many immigrants, including a substantial number of our Hispanic population,

5. An unacceptable level of child poverty in an affluent, industrialized society,

6. Rates of infant mortality and low birth weight in poverty and minority populations that are high, especially when compared with those of other industrial nations,

7. The worsening and highly visible homelessness problem and the increased proportion of children and adolescents with and without families within that population,

8. The high rate of adolescent pregnancy,

9. Growing concern about the large number of children who are physically and sexually abused, neglected, and emotionally disturbed,

10. A fragmented and inadequate system for providing ongoing care for emotionally disturbed children,

11. The national health insurance debate, which focuses on access to care (but, unfortunately, not on either quality of care or benefit to recipients). There is apparent legislative interest in the so-called Oregon plan, whereby care is prioritized and rationed and which is silent as to psychiatric care for children and adolescents.

This is an extensive (and only partial) list of legitimate and pressing concerns that have gotten, and are continuing to get, the attention of a great many people who come from different directions but whose courses converge on children's issues. Just as was the case 100 years ago, there is reason to believe that quantum gains can be made at this time. We in psychiatry rarely have this many actual and potential allies, and we should capitalize on this and be at the forefront when it comes to our children, our future.

Beyond our obvious obligation as parents, professionals, and citizens to provide a wholesome and meaningful childhood for our children, we have a further duty to equip them to flourish when the time comes for them to carry the mantle—for their own good, of course, but also to maximize the chances for a continuing healthy and productive future for all of us. We as psychiatrists, no matter what our subspecialty, recognize that the mental health of children inevitably has a profound impact on their adult lives. Many recognized adult psychiatric disturbances—depression, bipolar disease, schizophrenia, and panic disorder—begin in childhood. We can take heart, as Dr. Pardes reminds us, in the continuing advances in epidemiology, research, and clinical treatment that have made possible improved understanding, diagnosis, treatment, and prevention of childhood disorders. Yet our journals remind us that more children than ever

under the age of 18 suffer from mental illness and emotional disorder. The Institute of Medicine, in a scholarly study published last year (6), estimated that one-quarter of the U.S. population is under age 18 and that at least 12% of these children currently have a diagnosable mental illness. In other words, at least 7.5 million children under age 18 suffer from one or more mental disorders.

Moreover, more children under the age of 18 than at any time in the past live in foster care or in families shattered by separation, divorce, death, drugs, poverty, or some combination of these conditions. "No Place to Call Home: Discarded Children in America," a report of the U.S. House of Representatives Select Committee on Children, Youth, and Families (7), informs us that there has been a dramatic increase in the number of children placed outside of their homes during the decade of the 1980s. Many of these placements are appropriate. Children with mental health problems, who need and deserve mental health care, however, are frequently placed in the child welfare and juvenile justice systems where they can expect to find precious little mental health care and virtually no continuity of care. It is only the most fortunate of the children with mental health problems, in fact, who are in hospital or outpatient treatment.

Certainly an agenda for the 1990s must concern itself with availability of service. However, even before considering this problem, we should take a moment to remind ourselves of a few areas, more within the control of our profession, in which children, similarly, are not receiving their just due. For instance, *DSM-III-R*, a 500-page manual, devotes only 50 pages to disorders of infancy, childhood, and adolescence. The nosology of childhood disorders and diagnostic criteria are being reviewed and revised and, one hopes, will be clearer, more consistent, and more conceptually accurate. I am pleased that one volume of the *Treatments of Psychiatric Disorders* (8) is devoted to the multiple treatment modalities currently used by practitioners in their daily clinical work with youth. As we develop practice parameters, we must consult with our child psychiatric colleagues to ensure inclusion of the salient parameters for children. No good epidemiologic catchment area study dealing with the incidence and prevalence of childhood disorders is yet available, although such a study is in progress. In addition, there are still only a few good outcome studies in children.

I would be remiss if I concluded my comments about our housekeeping duties without stressing to our trainees the urgency of conveying the gratification and excitement of working with youth. Too few medical students are choosing psychiatry, and a study by the Graduate Medical Education National Advisory Committee (GMENAC) (9), as well as other studies, report a current shortage of residents trained in child work and predict a greater shortfall in the future. Can we ignore this?

Today's trainee will practice 30 to 40 years, and those who settle upon child psychiatry will travel the

road that Dr. Pardes envisions, incorporating the new diagnostic skills and therapies such as pharmacotherapy into the traditional techniques and skills such as play therapy, behavior therapy, and family therapy. Psychiatrists who understand child development can also make unique contributions by working with other medical specialists in pediatric wards, newborn intensive care units, and cancer units and with allied mental health professionals in the courts, welfare agencies, and the schools, whose role in the lives of our youth is ever increasing. For future child psychiatrists, the prognosis for career satisfaction is excellent.

Despite the encouraging outlook for primary, secondary, and tertiary prevention, diagnosis, and treatment, a fact that I have already alluded to is that few children obtain desperately needed treatment. Funding for care, both in the public and private sectors, continues to erode. This last year, in my travels around the country, I have seen the closing or proposed closing of public psychiatric hospitals for children. A new phenomenon—the deinstitutionalization of children—is leading to a new clinical population wandering the streets of our cities—homeless children. Just as deinstitutionalization did not lead to increased community programs for adults, it has not led to community programs for children. The promised increase in community funding never seems to materialize. Children, too, need day treatment, case management, home-based child and family services, respite care, family-based crisis and other emergency services, therapeutic group homes, and transitional services to allow young adolescents to achieve independent living.

Children with serious emotional disturbances need access to a wide range of services, but for most of them this continuum is simply not available. Inpatient and residential services are relatively well-funded only when compared to less restrictive programs, which are seriously underfunded or nonexistent in most communities. Interest in national health insurance is increasing as care for children and other dependents is being limited by private carriers. Thus, there is a fresh debate about how to include children and other dependents in any new health insurance scheme. The crisis of runaway costs and poor access to care has Congress, consumers, and even the media clamoring for solutions without any consensus in sight except, perhaps, the ancient panacea, discriminatory coverage for psychiatric patients.

Funding for care in the private sector has diminished as many insurance companies attempt to limit benefits with imaginative but specious theories. For instance, they claim the diagnosis of conduct disorder is a wastebasket diagnosis, and some professionals in other fields encourage them by maintaining that normal adolescents are hospitalized inappropriately. Although on occasion this may be the case, an unnecessary hospitalization is unlikely when a psychiatrist is responsible for the decision to admit. Similarly, some insurers contend that the diagnosis of drug and alcohol abuse leads to excessive and inappropriate care for adolescents

who are only in the midst of an unresolved period of adolescent turmoil and a developmental crisis. And, finally, I am concerned about the extent of the interest being expressed in the alarming idea of mandating coverage only for those illnesses that are clearly biologically based.

While a children's agenda for the 1990s will have to address many issues besides access to service, as our time today is limited, I will confine the balance of my remarks to just three of these—stigma, social causes of mental disorders, and violence.

I realize, of course, that 2 years ago we concentrated on stigma. But because I continue to feel strongly about this problem, I would like to reflect on it for just a moment today. Stigma remains an irrational blight on the lives of people who, obviously, deserve better, and I urge intensification of our efforts to remove it. Far too often, stigma attaches to children and their families who seek treatment. The stigma accompanying an emotional disturbance in childhood may easily follow the child through adolescence, adulthood, and maturity. It is both internal and external. That is, the child may feel guilty, damaged, and unworthy, and this perspective is likely to be shared by society.

Children frequently blame their parents for their illness. Parents blame the children. Society, sometimes in concert with our profession, is apt to blame both. Parents, natural allies of their children in the treatment process, nonetheless are often ignored or denigrated when it comes time for planning this treatment. We should remember that parents are often advocates, indeed, effective advocates, of programs that we endorse. They can be allies and systems of support for us, as well as for their children, in achieving a common objective with respect to effective treatment.

Now I would like to turn, albeit briefly, to a few thoughts about the social causes of mental disorders.

Of course, a variety of biological, psychological, and environmental factors are associated with the development of mental disorders and emotional disorders in children. But as we learn more about genetic defects; neurotransmitters; child development; and exposure to environmental toxins such as lead, trichloroethylene, polychlorinated biphenyls, and organophosphates, which either physically or emotionally afflict the child or a family member, we must not forget about the social causes of emotional disturbance—poverty; neglect; physical, sexual, and mental abuse; and the mental illness or loss of a parent or caretaker through death or divorce. These are all contributors to childhood mental illness.

We have devoted time, energy, and resources to a beginning study of the biological and genetic factors affecting children. The National Institute of Mental Health (NIMH), for example, has called for a new initiative in supporting a new cadre of child researchers in the biological causes of disturbance in children.

Although there is a substantial increase in the NIMH professional budget request for next year for children's mental health research initiatives, including

biological research and training researchers, it does not appear that any funds will be allocated for investigating the social causes of childhood mental illness. Nor will there be any provision for demonstration grants in the treatment of disturbed children whose case histories include any of the social problems associated with the development of mental illness. In our zeal to investigate and cope with the biological causes of mental illness, it is unwise to ignore social causes and psychosocial treatments. Therefore, I will continue to advocate, and urge others to advocate, funding for demonstration grants in the treatment and clinical research of disturbed children who have experienced any of these social problems.

Whether this kind of appropriation is forthcoming depends on our national priorities. The current administration has articulated worthy goals—reduced crime, reduced drug abuse, reduced teenage pregnancy, and reduced teenage suicide. Whether the government sees these objectives as sufficiently important to justify spending to achieve them, however, remains to be seen.

And what about violence? The increased prevalence in our society of both violence generally and violence in the family is alarming. Violent behavior in America, already at an all time high, appears to be increasing. With regularity, the media reports extraordinary forms of violence directed toward children—a child returned to the custody of his mother subsequent to her having given him a scalding bath; a youngster who is terrified because his father, who had set him on fire during a child custody dispute, is being released from prison. Each day, new and more spectacular violent acts are reported in the media.

In the past, we accepted the myth that violent acts were the problems only of the urban poor, young male minorities, school dropouts, persons from broken homes, and emotionally disturbed slum dwellers; that violent acts were common among them and their children, not us or our children. We now realize that violence can be found in affluent suburban neighborhoods as well as in urban ghettos and that it is not the exclusive prerogative of the lower socioeconomic classes. It is endemic and epidemic, a serious public health problem.

However, our ignorance in regard to its causes, prevention, and treatment with respect to both perpetrators and victims and the effect of violence on our children and their families is vast, and the subject is underresearched. Many of us avoid treating violent children or children and their families who have been exposed to violence, suggesting that their problems are only social, not medical in nature. Moreover, there is a new myth that we will find a single biological cause for violent behavior. The clue is to be found in blood, spinal fluid, or in the brain, so why not continue to ignore social causes? The truth is that there is no single cause of violence. Nor is there in the offing any one simple solution to solving the problems of such great magnitude that it causes.

It behooves us, then, if we are genuinely concerned

about the future, to inspire our trainees, residents, and fellows to accept the challenge that this situation presents and to do the necessary, but exciting, work in an area that has been largely neglected.

The 1890s' children's agenda signaled society's recognition that the well-being of children was the key to the development of a responsible adult citizenry. It was an agenda for the twentieth century, and many of its objectives were achieved. A 1990s' agenda, targeted on the social infrastructure of the twenty-first century, must again concentrate on the well-being of children, their physical health, and their mental health.

By focusing the annual meeting on our children, our future, I hope to call attention to problems of great magnitude that face our children and to challenge our profession, as did past Presidents, to take the lead in finding solutions. The fact that over the past 100 years we have developed modern, effective treatments, have supported and produced quality research, and possess impressive therapeutic skills should, of course, be a great encouragement. But to secure the future of our society, our commitment both to resolving the problems currently facing our youth and to continuing to treat children and adolescents and their families with care and compassion is imperative.

Senator Daniel Patrick Moynihan of New York, closing his series of lectures at Harvard on children and their families, observed that the future of a society may be forecast by how it cares for its young. Let that sentiment be a challenge to us. Who can foresee the achievements of psychiatry in the next hundred years? In the year 2090, let it be recorded that in the last years of the twentieth century the members of APA made a substantial investment in the future, a commitment to their children.

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Herbert Pardes, M.D.,
One Hundred Eighteenth President, 1989–1990

H. Keith H. Brodie, M.D.

E ven the barest outline of Herbert Pardes' early years reveals characteristics that have stayed with him throughout a crowded and successful professional life. Among these are commitment to the highest ideals of the healing profession, empathy for the suffering, determination, and broad interests that have developed an extraordinary talent for integration of perspectives and disciplines. As physician, scientist, teacher, and administrator, he has provided us a worthy model of the psychiatrist as a leader not only of psychiatry but of medicine as a whole.

Born in 1934 in the Bronx, N.Y., Herb Pardes grew up in Lakewood, N.J., where his parents owned and operated a hotel. He attended the public schools of Lakewood and during the summers helped his parents run a resort at the Jersey shore, taking his turn at such jobs as bellhop, concessionaire, busboy, and headwaiter. Because he was a bright student, Herb's family encouraged him to look toward an academic or professional career, but his choice of medicine was probably determined quite early by his experience, as a young child, with Perthes disease of the hip. At age 7, Herb was put in a toe-to-shoulder cast, which he wore for 10 months, followed by 2 years in a brace. Nonetheless, because his father believed that "nothing is impossible," he carried his son to baseball games and encouraged him to play while still wearing a cast and, later, the brace. The feeling of being at risk impressed the little boy, as did his father's "can do" attitude, and undoubtedly reinforced his later concept of medicine as both a noble profession and a practical avenue to solving painful human problems.

An outstanding student at Rutgers, which he attended on a scholarship, Herb was offered admission at the end of his junior year to the College of Medicine of the State University of New York, Brooklyn (Downstate Medical Center). But he recalls turning down the early acceptance because he realized, while listening to a piece of classical music, that he wanted to spend more time studying the humanities. After his graduation summa cum laude in 1956, Herb did matriculate at Downstate. There, he remembers being influenced

by outstanding teachers from the psychiatry department who fanned an interest in abnormal psychology that had been sparked at Rutgers. Herb's medical internship at Kings County Hospital, Brooklyn, provided convincing evidence of how medical, psychological, and social problems are intertwined in people's lives; this experience, combined with an innate curiosity about "how people tick," led to his subsequent residency in psychiatry, also at Kings County. Unfortunately, the Berlin crisis intervened, and Herb's psychiatric training took an unusual turn in 1962 when he was drafted. Herb was sent to Fort Myer, in Arlington, Va., where the former first-year psychiatry resident found himself chief of the U.S. Army Mental Hygiene Clinic. The event proved to be less a comic interruption, however, than a valuable opportunity, he says, to gain experience "evaluating top brass," supervising clinic personnel, and testifying as an expert witness.

In 1964 Herb returned to Kings County to complete his remaining 2 years of residency. During this time he also began training at the New York Psychoanalytic Institute (1965–1970), accepted a research fellowship and accompanying appointment as Director of Medical Science at Downstate (1965–1968), and began his private practice (1966–1978). Herb's swift progression at Downstate to Assistant Director of Residency Training (1968–1970), Director of the Psychiatric Division of the State University Hospital (1971–1972), and, finally, Professor and Chairman of the Department of Psychiatry (1972–1975) testify to his extraordinary talent for leadership. Relatively early in his professional life, he discovered that he had an aptitude for administration—an ability to see the big picture and a positive delight in quickly organizing the elements of a problem and devising solutions. Colleagues also cite his understanding of how organizations work and his quick political instincts. "Herb Pardes," says an old friend from Downstate days, "should have been a senator, not a psychiatrist."

Despite his relative youth, Herbert Pardes was able to bring to the administrative challenge a background in both research and psychoanalysis and a remarkable capacity to take the broad view, integrating research, education, and clinical work. At Downstate, a large and complex institution, Herb's enthusiasm and breadth nurtured a superb, eclectic department. One of Herb Pardes' great talents is his power to be a catalyst—he is able to draw people out, to get them involved and excited. The fruit of such a gift is multitu-

dinous, but one that should be singled out for its impact on medical student education is the textbook *Understanding Human Behavior in Health and Illness*, originally coedited with Richard Simons (who says Herb talked him into doing the book) and first published in 1977 (1). The two editors identified contributors whom they knew to be good teachers and persuaded them to write readable chapters that conveyed the human emotional experience as well as the most up-to-date information. Herb conceived of the book as "a way of passing on good teaching." This remarkable text has strongly influenced departments of psychiatry to give medical student education a high priority.

In 1975 Herb left Downstate to chair the Department of Psychiatry at the University of Colorado Medical Center in Denver, where he had been offered an irresistible opportunity to revitalize the department and revamp the curriculum. With 18 positions to fill, he was able to hire new people to meet his goal of building a diversified program, maintaining support for Colorado's psychoanalytic institute while advocating an increase in basic science research. An associate at Colorado notes the impact there of Herb's trademarks, eclecticism and speed: "He accomplishes a great deal very quickly and then moves on." From Colorado Herb was persuaded to move on by Health, Education, and Welfare Secretary Joseph Califano, who recruited him for the directorship of the National Institute of Mental Health (NIMH) (1978–1984). Herb characterizes himself during these years as one who "learned to be a federal bureaucrat," but a more accurate appraisal would find that Herb Pardes became this nation's leading advocate for the mentally ill and for the basic research that promises someday to alleviate and perhaps even cure the diseases that cloud their lives.

As Director of NIMH, Herb Pardes shaped the institute into a much more sharply focused, responsive, and effective support for American psychiatry. Having taken office with the encouragement of the Carter White House, and especially Rosalyn Carter, he nonetheless weathered the more austere days of the first Reagan administration, successfully fighting efforts to cut funds and presiding over an $84 million increase in the NIMH research budget (2). Herb bent his efforts to restoring the institute's credibility: unproductive programs were eliminated, service and education functions were clearly separated, the research portfolio was strengthened, and a new emphasis was placed on research in the neurobiological and behavioral sciences.

Among Herb's many contributions while director, one effort truly deserves to be called *pioneering*. Through his involvement with and outspoken support of citizen advocacy groups, Herb Pardes has contributed his leadership to one of the most significant mental health developments of the 1980s. As a newcomer to Washington, he quickly became sensitized to the role of lobbying groups in influencing the federal government, and to the need for constant education efforts directed at Congress and federal officials (3). Realizing the implications for the future of psychiatry, Herb ac-

cepted the role of advisor to the National Alliance for the Mentally Ill at its formation in 1979. Subsequently a charter member of the National Depressive and Manic Depressive Association and currently president of the scientific advisory board of the National Alliance for Research on Schizophrenia and Depression, Herb was one of the first among psychiatrists to recognize the potential of citizen groups to aid the cause of research in mental illness. The partnership of psychiatrists with the families of their patients is one that he believes in and has continued to champion vigorously since leaving NIMH. Certainly these citizen advocacy groups have given psychiatry a political voice that it never had before.

In 1984 Herb left NIMH to accept appointment as the Lawrence C. Kolb Professor and Chairman of the Department of Psychiatry at Columbia University, serving concomitantly as Director of the Psychiatry Service at Columbia-Presbyterian Medical Center and, until February 1989, as Director of the New York State Psychiatric Institute. In March of that year he became Vice President for Health Sciences and Dean of the Faculty of Medicine at Columbia's College of Physicians and Surgeons. At Columbia Herb once again found himself reconciling divergent psychiatric viewpoints, recruiting new faculty, and building an already distinguished department toward even greater achievements in research—in genetics, imaging technology, Alzheimer's disease, children's disorders, schizophrenia, suicide, and other areas of national concern and scientific promise. As President of APA, Herb has brought this continuing emphasis on the scientific as well as the humane basis of psychiatry to his Presidential columns in *Psychiatric News*, through reports from some of the best researchers in fields ranging from schizophrenia and genetics to Alzheimer's disease, eating disorders, and alcoholism. Equally significant has been Herb's own courage in taking strong stands on such controversial topics as AIDS, abortion, and animal rights.

Ever interested in the broad sweep of our profession, Herbert Pardes has spoken consistently throughout his career for psychiatry rather than psychiatrists. He has lived the values that he cherishes in our profession and so often cites—values of tolerance and respect for individualism, of openness and understanding. In his response to the Presidential address last year, Herb stated that he is proud of being a psychiatrist. I think it is fair to state for the record that psychiatry is very proud of Herbert Pardes.

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Special Article

Family Functioning and Major Depression: An Overview

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The authors review the evidence supporting the idea that the family plays a major role in the development and course of major depression. They find that the family pathology evident during an acute depressive episode continues after the patient's remission; that the course of depressive illness, relapse rates, and suicidal behavior are all affected by family functioning; and that children of depressed parents are at high risk for psychopathology. The authors explore unresolved issues regarding our understanding of the factors mediating the interaction between major depression and family functioning, concluding that there is evidence to support family and marital interventions, particularly in the treatment of depressed women.

(Am J Psychiatry 1990; 147:1128–1137)

T he importance of the role of the family in the development and course of major psychiatric illness has become increasingly recognized over the past 10 years. Patients with major psychiatric illnesses are spending more time with their families because of shorter hospital stays for acute episodes and deinstitutionalization policies that have forced these patients to rely more heavily on available family members. At the same time, in spite of the dramatic promises of pharmacotherapy, a substantial number of patients either fail to respond to pharmacotherapy or have residual symptoms requiring additional psychosocial care (1, 2).

The earlier focus on the families of patients with schizophrenia has now shifted to include interest in what happens to the families of patients with major depression and how aspects of the family life of depressed patients may in turn affect the depressive illness itself. Sufficient empirical work had been done in this area to warrant an overview of what we know in this new and increasingly important domain.

The purpose of this paper is to summarize what is known about the impact of depression on families during an acute depressive episode, how family functioning changes as the depressive episode remits, and what factors in the family environment of depressed patients contribute to recovery, relapse, and suicidal behavior. We will also review the impact of major depression on parenting as well as the effect that major depression has on the children of depressed parents. We will review the evidence for the effectiveness of family treatments for patients with major depression. Finally, we will identify several unresolved issues that may shed more light on the factors involved in these interactions and guide future directions in research. Our emphasis will be on methodologically sound studies that have assessed patients with major depression.

FAMILY FUNCTIONING DURING AN ACUTE DEPRESSIVE EPISODE

One of the problems in trying to study the relationship between family processes and a relapsing and remitting illness is that both the family and the illness are changing over time. It is critical, therefore, to establish time frames when the relationship can be examined, both to obtain a clearer perspective on issues of causality and to allow for legitimate comparisons with other studies. The two most logical time frames for such studies are during an acute episode and at the time of remission of symptoms.

There are now many studies documenting the impact that depression has on the families of depressed patients during an acute depressive episode. Two studies reported more than 15 years ago (3, 4) have paved the way.

Weissman and Paykel (3) studied the impact of the depression of 40 moderately to severely depressed female outpatients on their families. They found that these depressed women were more reticent in their communications, were more submissive and dependent, were less affectionate toward their spouses, experienced more friction, and argued more frequently with their husbands than did nondepressed control subjects. These women also experienced more friction with their children and were reluctant to discuss personal feelings.

Hinchliffe et al. (4) used direct observational assessment techniques to assess 20 depressed psychiatric inpatients and their spouses during acute depressive episodes. Couples including the depressed patients had greater levels of negative hostile behavior, more self-preoccupation, more negative tension (tense, stuttering, and emotionally tinged speech), and more attempts at controlling other people than did couples including nondepressed surgical control subjects.

More recent studies using varied patient groups and assessment procedures have also found that families of depressed patients experience substantial problems during the most active phase of the illness. These disturbances are evident over a wide range of family functions.

A unique study of 27 depressed female outpatients observed in their homes while interacting with their families (5, 6) found that these women displayed less problem-solving behavior than their husbands and were less self-disclosing in their families than nondepressed women (5). These depressed women and their families appeared to be locked into an interacting style that promoted high rates of aversive interchanges among family members (6).

Marital difficulties in depressed women were also identified in a study comparing family relationships in 50 depressed women and 40 nondepressed women from working-class families (7). The marriages of the depressed women were significantly worse than those of the control subjects, particularly because of the depressed wives' greater need for both intimacy and support.

Our research group (8) found that 43 depressed inpatients and their families reported significantly more dysfunction than did 29 nonpsychiatric control families, particularly in the area of family communications and problem solving. Sixty-four percent of the families of depressed patients felt that their overall functioning was impaired (9).

It is not surprising that during the acute phase of an illness the patient's family is upset and feels more strain than "normal" or control families. However, a number of studies suggest that depressive illness is associated with more family distress and impairment than are other psychiatric illnesses and some medical conditions.

In our studies, the families of patients with major depression consistently showed more impaired family functioning than families of patients with alcohol dependence, adjustment disorders, schizophrenia, or bipolar disorder (10). A similar finding was reported by Crowther (11), who compared family functioning in 27 inpatients with major depression with family functioning in patients with schizophrenia, bipolar disorder, anxiety disorder, and alcohol abuse. Crowther noted that depressed patients reported significantly more marital maladjustment and desired significantly more changes in their marriages than did the other psychiatric inpatients, findings confirmed by the patients' therapists.

A comparison with other chronically remitting and relapsing illnesses is also informative. Bouras et al. (12) found that depression had a much greater impact on the marital life of depressed outpatients from the patients' and the spouses' points of view than did rheumatoid arthritis or cardiac illness.

The presence of a depressed family member has a major impact on other family members. Increased attention is being given to the difficulties experienced by family members having to cope on a daily basis with a depressed relative. Coyne et al. (13) noted that over 40% of adults living with a patient experiencing a depressive episode were distressed themselves to the point of meeting criteria for therapeutic intervention. Family members found the patient's lack of interest in social life, fatigue, feelings of hopelessness, and constant worrying to be the aspects most disturbing for them. The burden on family members was felt most substantially during the acute episode. Fadden et al. (14) found that the negative effects rather than the florid symptoms of mental illness were the most problematic for family members, who resisted attributing the patients' worrying, social withdrawal, irritability, and nagging to the mental illness itself.

In sum, studies using various methodologies and fairly diverse groups of patients have consistently shown that during an acute episode the families of patients with major depression experience substantial difficulties in many areas of their family life. Communications in the family are particularly problematic, especially appropriate self-disclosure by the depressed patient. Depressed women tend to be aversive to others and exhibit impaired parenting; the families as a whole experience difficulties in their ability to solve problems. Overall, the families of depressed patients appear to experience more difficulties than do families of patients with schizophrenia or bipolar illness or families of patients with rheumatoid arthritis or cardiac disease.

FAMILY FUNCTIONING AT REMISSION

The finding of family disturbances during acute depressive episodes leads to the following questions. Do the difficulties reported during an acute episode reflect the family's response to the patient's depression or do they represent a more chronic pattern of family dys-

function? More specifically, does family functioning change after recovery from the acute episode? If so, does family functioning return to a "normal" level after the acute episode has been resolved?

Studies of depressed outpatients (15–17) as well as inpatients (9, 18, 19) have shown that family functioning improves as depression remits, although the families still experience more dysfunction than nonclinical families. They still report significantly poorer functioning than control families, particularly in their ability to solve problems, to communicate with each other, and to feel generally satisfied with their overall functioning (9).

In general, there is striking consistency in the findings of studies that have examined changes in family functioning as a depressive illness remits. Even as depressive symptoms decrease and family functioning improves over time, these families continue to experience more problems than nonclinical families. It seems evident that continued work with and support for these families are warranted even after the depressive episode has subsided. It is still not clear, however, to what extent the ongoing problems in these families are a function of the depressive illness itself rather than other factors.

FAMILY FUNCTIONING AND THE COURSE OF DEPRESSIVE ILLNESS

Recovery

A further question concerns the relationship of family functioning to the course of depressive illness. Is family functioning associated with recovery rates? More specifically, are patients with poor family functioning during the acute phase of the illness more likely to have a slow rate of recovery? Does change in the quality of family life have any bearing on the course of depressive illness? Only four studies (9, 20–22) have addressed this issue.

Rounsaville et al. (20) reported that a reduction in the number of marital disputes was associated with improved depressive symptoms and social functioning after 8 months of individual psychotherapy in depressed female outpatients. From a different perspective, Corney (21) noted that women who had major marital problems were more likely to be depressed at follow-up than those with good relationships and that women with no or minor marital problems improved more quickly than those with marital difficulties.

We found that among depressed inpatients who had recovered, those patients with families who improved in their general functioning had a significantly shorter time to recovery (4.1 months) than patients of families who did not improve (8.1 months) (9). Also, patients in families that improved in their communication, roles, and affective involvement showed nonsignificant

trends toward having a shorter recovery time. Therefore, although family functioning during an acute episode was not associated with speed of recovery among recovered patients, positive changes in overall family functioning during the course of illness were associated with faster recovery times.

Swindle et al. (22) assessed the effects of psychosocial factors on the course of unipolar depression in a large group of outpatients and inpatients (N=352). Assessments were made during an acute episode and at 1-year and 4-year follow-ups. Swindle et al. concluded that a concurrent medical condition in the patient and family conflict at the index episode consistently predicted poorer long-term outcome for the depression.

Despite the very limited number of studies that have investigated the relationship between family functioning and recovery from depression, the available data suggest that problematic family functioning is associated with lower rates of recovery and slower recovery among patients who do recover. However, it is not possible to distinguish whether this association between family functioning and recovery occurs because impaired family functioning affects the patient's depression or because a chronic course of depression produces greater family impairment.

Relapse

Another critical question is whether the quality or type of family functioning is associated with relapse. That is, are patients in certain family environments more likely to have higher or lower rates of relapse? Two studies (23, 24) have investigated this issue.

Vaughn and Leff (23) reported that depressed patients whose family members had high levels of expressed emotion—critical, hostile, or emotionally overinvolved attitudes expressed by key relatives in reference to the depressed patient—were three times as likely to relapse within 9 months as were patients whose relatives had low levels of expressed emotion. Similar results were found in a replication study by Hooley et al. (24). Over a 9-month follow-up period, Hooley et al. found that 59% of the patients whose spouses had high levels of expressed emotion relapsed but that no patients living with spouses with low levels of expressed emotion did so. Furthermore, depressed patients tended to relapse at lower levels of criticism than did schizophrenic patients. Interestingly, of the nine patients in homes with high levels of expressed emotion who did not relapse, seven were men.

Expressed emotion is time-consuming to measure. In an attempt to find related but more easily assessed relationship variables that may predict relapse in depressed patients, Hooley and Teasdale (25) examined the predictive utility of two other family measures— marital distress and perceived criticism—in the same group of patients used to study expressed emotion (24). Marital satisfaction was measured by using the Dyadic Adjustment Scale (26). Perceived criticism was

assessed on a 10-point Lykert-type scale in response to the question, "How critical is your spouse of you?" Although all three family variables were significantly associated with 9-month relapse rates, the single best predictor of relapse was the patients' views of their spouses' criticalness. These results strongly suggest that a simple way to identify depressed patients at high risk for relapse is to ask them how critical they feel their relatives are toward them.

It is becoming increasingly apparent that a supportive, nonstressful social environment is important in sustaining remissions. Provoking factors like stressful life events are associated with a higher risk of relapse, especially in the presence of long-term vulnerability factors such as lack of supportive social networks (27) and even independent of frequency of depressive symptoms (16). Although conflict in the family is associated with relapse, an open supportive discussion of feelings and problems in the family may predict lower rates of rehospitalization (28).

Again, despite the limited number of studies, the available data suggest that the family environment in which depression evolves does have a substantial relationship to the likelihood of recurrence of a depressive episode. A stressful, unsupportive, and, particularly, a critical social environment have been found consistently to be associated with a higher rate of relapse. However, as with the relationship between family functioning and recovery, it is impossible to separate cause from effect in these studies.

SUICIDE AND FAMILY FUNCTIONING

Studies focusing on familial factors in suicidal behavior have tended to explore genetic associations, loss of family members, and nonspecific family stresses (29–31). Very few studies have attempted to assess the intrafamilial environment within which suicidal behavior emerges.

Our research group found that depressed inpatients who attempted suicide perceived their family functioning to be worse than did their families (32). Suicidal patients also viewed their families more negatively than did depressed nonsuicidal inpatients, who actually viewed their family functioning more positively than did their family members (32).

In a 2-year follow-up study (33) we attempted to delineate which psychosocial factors were related to subsequent suicide attempts in depressed patients. We found that previous suicide attempts, interepisodic adjustment, changes in family constellation, and a negative perception of family functioning were characteristic of depressed patients with recurrent suicide attempts.

Although suicide attempts are certainly multidetermined acts, family functioning may be one of the important influences that help to explain why a minority of depressed patients attempt suicide while the majority do not.

CHILDREN AND PARENTING

The repeated findings of impaired family functioning in patients with major depression raise additional questions. What happens to the children of depressed parents? How is their upbringing affected by the patient's depression? Are these children at higher risk for psychopathology? Is the greater risk of psychopathology in these children a function of their parents' specific illness or is it a nonspecific effect of distress in the family?

A number of review articles (34–36) have concluded that 1) depressed parents have impaired relationships with their children, 2) these impairments are greater in the families of depressed patients than they are in the families of nonclinical subjects, 3) there is a negative relationship between a parent's depressive mood and a child's functioning, and 4) the homes of depressed children are characterized by family discord and parental rejection.

An increasing number of controlled studies have looked at the issue of the impact of parental affective disorder on children. The results of these studies (37–43) have been very consistent with previous findings of the negative impact of parental depression on children.

Rates of major depression in the children of parents with affective disorder range from 23% to 38%, in contrast to ranges of 11%–24% in control families; rates of any DSM-III diagnoses in children of depressed parents range from 65% to 73%, as opposed to 52%–65% in control families (40, 44, 45). In addition, it has been noted (40) that children of depressed parents have a younger age at onset of depression (12–13 years) than do children of normal parents (16–17 years).

It is not clear to what extent a child's psychopathology is a function of the parent's depressive illness or of the presence of any psychiatric or medical disorder (38, 39, 41). Generally, psychiatric illness appears to create a greater burden than do nonpsychiatric illnesses (43), but this may not be specific to depression. The severity and chronicity of the parent's illness also have substantial effects on the child's psychopathology and functioning (41, 44).

From a different perspective, depressed women complain of difficulties in coping with unruly and disobedient behavior in their children (7). They also report high levels of inconsistency in discipline and control and tend to be highly protective of their children (39). It may be that a positive family environment (low levels of stress and high levels of support) is associated with lower rates of disturbance in the children (37). However, even in families where the parent's depression is remitted, children still function more poorly than do children in nonclinical control families (46).

Overall, the findings of these studies are consistent in highlighting the substantial impact that major depression in a parent has on the functioning of children

in these families. These children appear to be at much higher risk not only for affective illness but for psychopathology in general.

The cause of the higher rate of psychopathology in children of depressed parents is not clear. Both genetic and psychosocial factors have been hypothesized to be relevant (47, 48). Genetic vulnerability has been most clearly established for severe unipolar depression (49). However, no studies have been conducted comparing the relative strength of genetic and psychosocial factors. Similarly, the direct contribution of family environment to child psychopathology has not been investigated. Despite this lack of direct evidence, it seems reasonable to hypothesize that there is an interactive effect among genetic vulnerability, deficient parenting skills, and overall family environment which contributes to the psychopathology in the children of depressed parents. Specific parental diagnosis, severity and chronicity of the affective illness, and the nonspecific stresses and strains brought about by having an ill parent appear to increase the risk.

TREATMENT

Since evidence for the substantial impact that depression has on the families of depressed patients and the role of the social environment on the course of depressive illness has only recently been established, it is not surprising that there are few controlled studies of family interventions with patients suffering from major depression.

One of the earliest studies of marital treatment for patients with depression was undertaken by McLean et al. (50). Their purpose was to determine whether a behavioral approach to the treatment of depressed patients and their spouses, with particular emphasis on modification of verbal interactional styles in addition to social learning training using behavioral contracts, would be more effective than standard community treatment. The experimental group receiving the behavioral marital treatment showed a more significant reduction of problematic behaviors, depressive symptoms, and negative actions and reactions than did the comparison group. In another study using small numbers of patients, Beach and O'Leary (51) noted that marital therapy showed promise in alleviating both depression and marital discord.

In the first well-controlled study comparing the effectiveness of an antidepressant drug (amitriptyline), marital therapy, and the combination of the two, Friedman (52) found that the combination of the drug and marital therapy was more effective than either treatment administered separately. Drug therapy was faster and more effective in relieving symptoms and clinically improving the depression, and marital therapy was more effective in improving role task performance and perception of the marital relationship. Importantly, the patient group that received amitriptyline and marital therapy showed more improvement than any of the other three groups (drug plus minimal contact, placebo plus marital therapy, placebo plus minimal contact).

A randomized clinical trial of family intervention for inpatients with schizophrenia or affective disorders was undertaken by the family research group at the Payne Whitney Clinic (53–55). This study attempted to determine whether the inclusion of a family intervention package added any benefit to standard hospital treatment. The family intervention consisted of six psychoeducational family sessions over a 5-week hospital stay. These sessions were reality oriented and dealt with practical problems. The standard hospital treatment included a diagnostic workup, group therapy, milieu therapy, activity therapies, and pharmacotherapy. Patients were randomly assigned to hospitalization with or without the inpatient family intervention. The family intervention was provided by a social worker on the unit together with the psychology intern or psychiatry resident. Overall, the study found that at discharge from the hospital the inpatient family intervention had a positive effect on female patients with schizophrenia or affective disorders and their families. This positive effect was sustained at 6- and 18-month follow-up. Surprisingly, not only was there no benefit but actually a slight worsening found with the family intervention for male patients.

Marital therapy may be selectively helpful for depressed patients who are involved in problematic relationships. In an unpublished 1987 paper, Jacobson et al. reported that patients with marital problems had lower relapse rates when given a treatment package including marital therapy and that patients without marital problems did not require marital intervention.

Group therapy with the families of patients with major depression has become increasingly popular over the past 5 years. In an attempt to tease out the active ingredients in these large-group formats, Anderson et al. (56) randomly assigned inpatients with affective disorders and their families to either a multiple-family group with a process orientation emphasizing support and self-help or a psychoeducational group emphasizing information about the illness. Both types of groups were found to be useful and desirable for the inpatients; very little difference was found between the two formats. The families of the patients receiving the psychoeducational program, however, were more satisfied with their experience.

In summary, preliminary evidence suggests that adding a family approach to the treatment of major depression may be helpful, especially for depressed female patients who are experiencing marital turmoil. Further research in this area is sorely needed, given the paucity of well-designed studies, the prevalence of the disorder, and the substantial family dysfunction associated with it.

UNRESOLVED ISSUES

It is evident from the literature reviewed that the families of patients with major depression have substantial impairments in family functioning during acute depressive episodes and also during remissions. Several issues remain unresolved and need further clarification, however. Particular issues requiring further study relate to the heterogeneity of depressive families, the congruence among perceptions of different family members, the instruments used to assess family functioning, sex differences in depressive illness, and the causal relationship between family functioning and major depression.

Heterogeneity

Although *DSM-III* has helped to define depressive illness more precisely, major depression most likely consists of a number of different disorders. In addition, the psychopathological problems of patients with major depression and of their families (57) differ clinically. At present, there is little research support for the hypothesis that a particular family constellation or interactional style invariably leads toward or is associated with major depression. Factors such as the premorbid functioning of the family, the developmental stage of the family, the health of other family members (particularly the presence or absence of psychiatric illness), the family's social and financial situation, and the availability of external supports may all bear on the family's level of functioning and capacity to deal with crises, including an affective episode. The issue of assortative mating (58) may also influence the burden felt by other family members and the support available to the depressed patient.

Nonfamily factors may also have a major impact on a family's response to depressive illness. There is marked heterogeneity in the patients themselves. Notable complicating factors are the finding of concurrent dysthymia and/or personality disorders of various types (59, 60). What is the importance of the presence of such coexisting axis II diagnoses (61, 62)? Some depressive disorders coexist with a variety of other axis I and axis III disorders as well. This comorbidity has been found to have an additional deleterious effect on family functioning and on recovery rates (22, 63). Most of the literature on comorbidity of depression and medical conditions explores the prevalence of depression and its impact on a variety of medical illnesses. Few have focused on the impact of medical illnesses on depression.

Current studies have paid little attention to these issues of heterogeneity. However, in the absence of studies investigating the relationship between family functioning and these other characteristics of depressed patients and their families, it is not clear whether family dysfunction is an independent prognostic factor or is an epiphenomenon strongly associated with other particular features or subgroups of depressed patients. This question has important implications regarding the most appropriate focus of treatment interventions. Studies investigating these issues are clearly needed.

Measurement of Family Functioning

One of the difficulties in reviewing studies of depressed families is that many different instruments are used to assess marital and family satisfaction, adjustment, and functioning. It is beyond the scope of this paper to review all of these instruments. Some are well validated and psychometrically tested (64–68). Others were not primarily designed or validated to assess family functioning, although some of their subscales have been used for that purpose (69). Still others were designed for a particular study and do not have much psychometric support (70, 71). The instruments range from questions concerning general satisfaction (26, 68) to schedules assessing multiple aspects of family life (64–66, 72). The relative validity of the results reported is very difficult to assess accurately.

It is unclear whether the same or similar family processes are being measured in these studies and to what extent the findings from the different studies can be merged. It is all the more striking, therefore, to note the remarkable uniformity of findings in different studies using widely disparate measures. Generally, almost all studies agree that families of depressed patients experience substantial disturbances through all of the stages of the illness.

A second problem in the assessment of families is that very few studies have actually attempted to evaluate family functioning using objective measures. Most studies have used the perceptions of family members as a reflection of family functioning. Only a few have attempted to observe and rate these families using trained interviewers (4, 24); fewer still have attempted to observe depressed patients in their own home environments (5, 6). Without such studies, it is difficult to separate actual family dysfunction from potential negative biases on the part of depressed patients.

Congruence of Perceptions Between Patients and Other Family Members

In describing and measuring family functioning, the issue of weighing the varying perspectives of family members creates a difficult methodological problem. Should one describe each family member's perception and give each equal weight? Should this be the same whether there are two family members or six? Should the same weight be given to the perceptions of children as to those of parents or grandparents? There are no easy answers to these questions.

Overall, studies have suggested that there is in fact good congruence between a depressed patient's description of his or her family functioning and that of other family members (19, 46).

For the sake of simplicity, our approach has been to

use mean family scores in our preliminary analyses. Discrepancies between the patients' perceptions and those of other family members, however, can be an important indication of particular types of problems. We have found, for instance, that a discrepancy in perception of the family environment between the depressed patient and other family members is strongly associated with suicide attempts (32).

At this point, we do not know the best way to report family assessment measures. Further research is needed to determine not only how common agreement between family members is but what disagreement implies for the course of the illness, potential for relapse, and other clinical or theoretical issues.

Sex Differences

The suggestion of differences in the responses of male and female patients to depressive illness is of considerable interest. It is well-known that the prevalence of depression in women is two to three times higher than it is in men (73). Partly because of this disparity, most studies investigating depression and family functioning have focused on female patients. The few that have not have provided mixed results in terms of differential patterns between men and women in response to a depressive episode (6, 11, 18, 38, 44, 55).

Overall, marriage appears to be less protective for women than for men (74). Married men, for instance, have consistently lower rates of affective disorders than single men, but married women do not have lower rates than single women (75). The woman's role also appears to be more critical than does the man's in terms of the impact of depression on children. A father's depression has no effect on the attachment between his children and their mother (38) and has a negligible association with his children's adaptive functioning (44). Given the disproportionately important role of women and mothers in families, perhaps it is not surprising that children in families with depressed mothers direct more aversive behavior at the mothers than they do at the fathers (6).

Consistent with these findings, depressed men tend to rate their marriages as significantly better adjusted than do depressed women (11). As the depression resolves, depressed men tend to show a greater shift in reducing tension with their partners than do depressed women (18).

It is interesting to note that family interventions not only may be more successful when the patient is a woman but may actually lead to some worsening with male patients (55). It may be that female patients need greater support in order to maintain their multiple role functions within the family.

The question of sex differences in depression remains unresolved (76) but certainly deserves further research. Attempts should be made to study more families with a male depressed patient to delineate more clearly what happens in these families and how they differ from those with a female depressed patient. In particular, the suggestion that differential treatment interventions may be indicated depending on the sex of the identified patient needs to be pursued.

Causality

It is not certain whether problematic family relationships predispose to or facilitate the emergence of depressive illness or whether the depressive illness and its attendant impact on patients' interpersonal styles create family difficulties in coping. There is evidence to support both points of view. In addition, the combination of a number of different stressors can obviously have an additive effect in leading to family dysfunction. Rounsaville et al. (15), for instance, suggested that the marriages of depressed women tended to be either good or disturbed over time. They also found that when women who had had disputes with their husbands divorced and remarried, they had disputes with their new husbands as well. Since a number of depressed patients are able to sustain good marriages, the personality of the depressed person rather than the illness itself may be responsible for the marital strain.

The individual characteristics of depressed patients may create problems for family members, rather than the family environment being destructive to the patient (6). The patient's level of depression may be less involved in creating family and interpersonal disturbances than factors intrinsic to the situation and the personalities of the family members involved (77, 78). In fact, there is evidence to suggest that marital distress itself may affect the severity of depression (79). Up to 70% of depressed patients reported that their marriages were poor before the onset of depression (80, 81). A variety of factors that are antecedents or sequelae of depression may lead indirectly to depression through their effect on the quality of the marital relationship (82).

In fact, the question of causality may be the wrong question to ask. There is no reason to assume a single linear relationship between depression and family functioning. It seems more likely that a mutually reinforcing negative pattern of interaction between patient vulnerability and family competence may prove a more useful model (see figure 1).

For a variety of reasons, certain patients are vulnerable to developing major depression. Their vulnerability may be genetically based and may be precipitated by a number of factors, such as illnesses, life events, personality variables, and early life experiences. On the other hand, there is a range of competence within families that is influenced by a variety of factors, including socioeconomic status, family composition, availability of social support, presence or absence of other psychiatric and/or medical illnesses, and current life events.

A patient's vulnerability may be readily influenced by family issues and forces at play at a given time. By the same token, a family's competence may be com-

FIGURE 1. Depression Model: Interaction Between Patient Vulnerability and Family Competence

PERSONALITY FACTORS	LIFE EVENTS		SOCIOECONOMIC STATUS	LIFE EVENTS
↓	↓		↓	↓

EARLY LIFE EXPERIENCES → **PATIENT VULNERABILITY** ←→ **FAMILY COMPETENCE** ← FAMILY COMPOSITION

↑	↑		↑	↑
GENETIC INFLUENCES	OTHER ILLNESSES		ASSORTATIVE MATING	SOCIAL SUPPORT
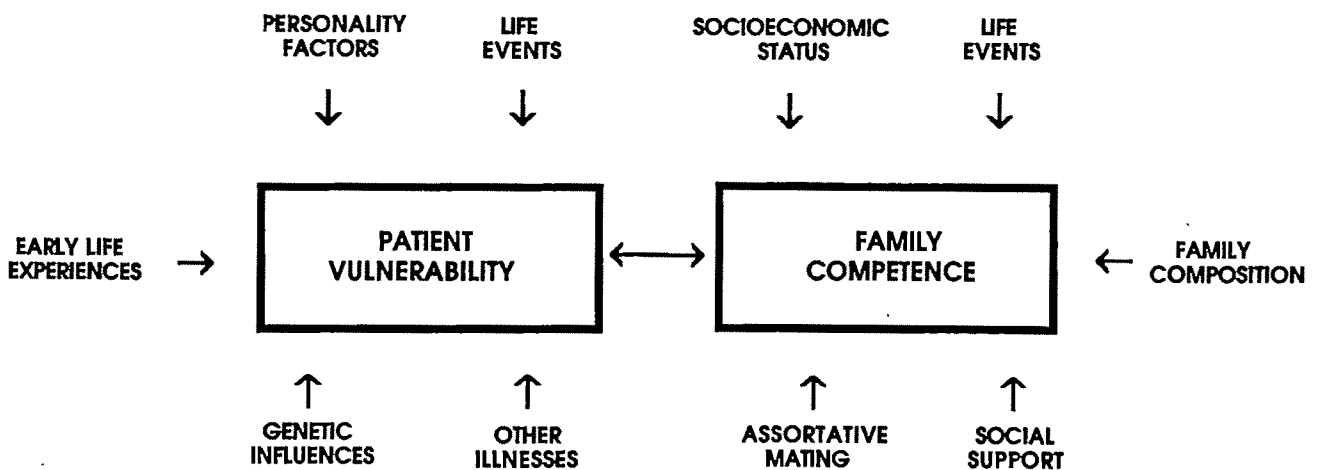
promised greatly by the illness, particularly an affective illness, of one of its members.

According to this model, then, a patient who is vulnerable to major depression develops a depressive episode. The depressive episode may have been caused by a variety of factors including family dysfunction. The family is now in the position of having to respond to the patient's illness. If the family is able to respond effectively, the depressive illness may last a relatively short time and may more readily remit. Conversely, if the family is unable to respond adequately to the patient's affective illness because of its own difficulties, there is evidence to suggest that the depressive episode will be prolonged and the patient will be more likely to relapse into subsequent episodes of depression. These subsequent episodes of depression may further impair the family's competence to cope, thereby setting up a vicious cycle. Patient vulnerability and family competence, therefore, can be seen as mutually reinforcing forces that may act either to further the depressive illness or provide a way of lessening its impact and tendency to recur.

This model not only allows for but in fact calls for interventions that address both the patient's vulnerability and the family's competence. The patient's vulnerability can be diminished with the aid of individual psychotherapy and psychopharmacological agents. The family's competence can be reinforced through the use of family intervention techniques, including psychoeducational groups, family therapy, and self-help support programs. The critical point is that both aspects of the system need to be addressed to deal adequately with this mutually reinforcing pattern.

CONCLUSIONS

What do we know about the relationship between major depression and family functioning? The available evidence supports a number of conclusions. Sub-stantial family dysfunction is a common accompaniment of an acute depressive episode. Even with remission of the depression, family strain often persists. Ongoing family problems, particularly if manifested by excessive criticism of the patient and an unsupportive family environment, are associated with a prolonged course of the depression, a greater tendency to relapse, and possibly a higher risk for suicide. Children of depressed parents are at high risk for both affective and nonaffective psychopathology.

It seems evident that the family system should be understood and worked with when treating a person with major depression. Unfortunately, it is not clear at this time what particular types of family approaches are most appropriate and for which patients. Studies assessing the usefulness of adding family therapy to the pharmacological and individual psychotherapeutic treatment of major depression are needed.

In the meantime it seems reasonable to develop a heightened awareness of the social context in which affective illness emerges and evolves. There is a danger of losing sight of this broader psychosocial reality with our increasing focus on neurochemical, neurophysiological, and pharmacological issues in the understanding and treatment of depressive illnesses.

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Regular Articles

Continuous Versus Targeted Medication in Schizophrenic Outpatients: Outcome Results

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The authors report on the outcome of treatment of 116 outpatients with chronic schizophrenia who were assigned to a 2-year, single-blind course of treatment with either targeted or continuous medication. These patients were not restricted to those who were good candidates for a medication reduction strategy. Continuous medication was superior to targeted medication in preventing decompensations and hospitalizations and in extent of employment at 2 years. Other measures of psychopathology and functioning at 1 and 2 years did not differentiate the two groups of patients. The targeted approach achieved a substantial reduction in total medication through a reduction in the number of days of medication administration.
(Am J Psychiatry 1990; 147:1138–1148)

The efficacy of neuroleptic drugs for reducing symptoms and preventing relapse in schizophrenia is clearly established and widely accepted. However, there is growing appreciation of the limitations and drawbacks of these agents. They carry a risk of substantial side effects, including severe movement disorders, which correlates with lifetime exposure (1). In

addition, important aspects of the psychopathology of schizophrenia, such as deficit symptoms, respond poorly to or may even be exacerbated by neuroleptics (2–4). Consequently, there has been increasing interest in developing viable clinical management alternatives to long-term, high-dose neuroleptic drug maintenance and prophylaxis. One approach explored by some investigators is the use of continuous medication at doses considerably below those traditionally viewed as therapeutic (5–8). Using a noncontinuous, or intermittent, approach, we and others have attempted to reduce cumulative neuroleptic doses by administering medication only during episodes of symptom exacerbation (9–13).

The rationale for the intermittent, or targeted, approach has been detailed elsewhere (10, 14, 15). Considerations supporting the plausibility of a targeted-medication approach include the episodic nature of psychotic symptoms in many schizophrenic patients and the fact that during remission neuroleptics have primarily a prophylactic function (16). In addition, identifiable symptoms and/or behavioral patterns typically presage psychotic episodes (14, 17–19), allowing time for rapid reintroduction of neuroleptic medication in an attempt to abort a full psychotic relapse. Finally, observations of two prominent European clinicians, Bleuler (20) and Ciompi (21), revealed that good outcome in the long-term was not dependent on the continuous administration of neuroleptic medication.

In the first uncontrolled trial of the targeted-medication approach, Herz et al. (9) evaluated targeted medication as an alternative to maintenance medication in a group of stable schizophrenic outpatients who had successfully completed an 8-week drug washout period. During the experimental treatment phase, which included group therapy, medication was admin-

istered under increased psychiatric surveillance only when a patient experienced early signs of relapse. Patients were closely monitored for prodromal signs, especially at times of stress, and significant others assisted in the observation process. Overall findings based on the treatment and nonblind observation of 13 stabilized patients over periods ranging from 13 to 45 weeks demonstrated the feasibility of the targeted-medication approach.

We reported preliminary data from the first controlled study of targeted medication in 1983 (10), and we reported the final results of the first phase of this project in 1987 (12). In the latter study we compared patients randomly assigned to either continuous drugs and standard clinical care (N=21) or targeted medication and enhanced psychosocial treatment (N=21). Outcome results of the 2-year trial were similar for the two groups of patients, but substantial drug reduction was accomplished in the experimental group.

The most recently reported study of the targeted drug approach is that of Jolley et al. (13), who conducted a double-blind, controlled trial of placebo versus standard-dose fluphenazine depot injections in the treatment of two groups of 27 randomly assigned remitted schizophrenic outpatients with good prognosis. Over a 1-year study period, oral haloperidol was administered to all patients when prodromal symptoms occurred. Treatment of these symptoms continued for up to 2 weeks unless relapse occurred; treatment of relapse was continued until 4 weeks after the remission of symptoms. Although prodromal episodes and relapses (the recurrence of schizophrenic symptoms) were more frequent in patients given placebo injections, only three placebo patients were hospitalized during the 1-year study; two patients given continuous fluphenazine were hospitalized during this period. Despite the higher rate of recurrence of psychotic symptoms in the placebo- or intermittent-treatment group, there were no overall differences between this group and the group that received fluphenazine maintenance in regular bimonthly ratings of psychotic symptoms and global assessments of psychopathology and social functioning. Although requiring more oral medication, the intermittent-treatment group, as expected, was given significantly less total medication (in terms of haloperidol equivalents). This group also experienced fewer extrapyramidal side effects and showed a trend toward less tardive dyskinesia. The investigators viewed their findings as an indication that intermittent treatment is a viable alternative to continuous oral or depot treatment for schizophrenic patients who are less ill and clinically stabilized.

The general hypothesis prompting clinical trials of targeted administration of antipsychotic drugs to patients with schizophrenia rests on two propositions: 1) that targeted drug administration is an effective alternative strategy and 2) that benefits are associated with medication reduction. We previously demonstrated an extensive similarity over a 2-year course of treatment between targeted medication embedded in enriched psychosocial clinical care and standardly administered continuous medication (12). The feasibility of the targeted-medication approach having been determined in that initial work, the primary aim of the present study was to isolate the comparative pharmacological effects of targeted versus continuous administration of medication by implementing both procedures within a context of enriched psychosocial care, with emphasis placed on early intervention in cases of relapse.

METHOD

This single-blind, randomized block, longitudinal study compared the efficacy of two pharmacological strategies, targeted and continuous administration of medication, in the treatment of schizophrenic outpatients over a 2-year period. A placebo control group was not used in the study design for reasons that seemed persuasive at the time of initiation of the study. To answer questions with regard to cooperation and feasibility associated with the targeted administration of medication and to obtain baseline information about the frequency of appearance of prodromal symptoms under drug-free conditions, we felt it important that targeted medication be prescribed as it would be in actual clinical practice. In addition, because the approach was dependent on early recognition of symptoms, we felt that both patients and their relatives would be especially vigilant in the recognition of change in symptoms and/or functioning if the patients were not receiving placebo medication. To minimize bias in the evaluation of outcome, assessments were completed by an evaluator blind to the treatment administered in any given case.

Subjects

Most of the patients in our outpatient program are accepted for evaluation and treatment on discharge from a psychiatric hospital unit; some patients are referred from a community clinic or practicing psychiatrist. The shared starting point in the study was that all patients had had a recent psychotic episode and were in some intermediate stage of recovery. Patients were referred from a variety of sources, but the majority of referrals were from the two state psychiatric hospitals serving the immediate geographic area.

Patients who had been psychotic for less than 2 weeks and who showed no evidence of prodromal or residual symptoms were not accepted for the study. Other exclusion criteria included evidence of an organic brain disorder, recent evidence of alcoholism or clinically significant drug abuse, poor physical health, a recent history of a major medical illness, or a substantial language or hearing problem that would interfere with participation in evaluation or treatment routines. Patients were selected as appropriate for long-term neuroleptic therapy but were not specifically defined as good candidates for drug reduction.

Pending suitability and mutual agreement, the patient and either a family member or significant other were seen by the outpatient clinic staff for further screening assessment, explanation of the study, and the obtaining of informed consent. Those patients accepted for study were scheduled for a clinic appointment after they formally indicated their agreement to participate by signing a written consent form meeting both federal and university regulations.

Evaluation and Treatment Procedures

Initial clinic visits were devoted to evaluation and stabilization, which generally involved a period lasting from 4 to 8 weeks, depending on the patient's clinical condition. The patient was seen on a weekly basis by a clinic staff member at the master's degree level who served as both an evaluator and clinician, providing therapeutic intervention as needed to help with problems and crises arising during this preliminary phase of the program. During a series of interviews, this initial contact staff member obtained a psychiatric and personal history and performed a mental status examination. A physical examination, including routine clinical laboratory tests and emphasizing the assessment of abnormal movements, was also conducted by a psychiatrist during this period, as were structured assessments of prognosis and psychopathology using both patient and family interviews as sources of information. Early in the preliminary phase, a psychiatrist was assigned to the patient to provide management of medication on a weekly basis. Patients were routinely receiving neuroleptic medication when referred to the clinic and generally continued to receive the same medication. In each case, an attempt was made to stabilize doses within the 4–8-week stabilization period. At the end of the stabilization phase, patients were randomly assigned within sex, age, and prognostic categories to either the targeted-medication or the maintenance-medication condition.

When a patient was clinically stable and felt comfortable with the outpatient clinic routines, medication was withdrawn abruptly to allow a 4-week drug-free period, during which assessments of emergent dyskinesia (22, 23), clinical baseline evaluations, and formal diagnostic schedules were completed. The clinical status of each patient was closely monitored during this drug-free phase, and additional support and more frequent staff-patient contacts were provided as needed. Neuroleptic medication was administered only when there was an obviously emerging clinical decompensation. When this occurred, the patient was restabilized before again attempting to complete the baseline drug-free phase. On successful completion of either the first or second drug-free trial, the patient entered the experimental phase. A patient failing to complete the drug-free period after two attempts was admitted to the experimental phase while receiving medication. If assignment of such a patient was to targeted medica-

tion, subsequent discontinuation of medication was prescribed according to the guidelines for this procedure. Since we were interested in longer-term treatment, the duration of the experimental treatment phase was set at 2 years.

The enriched psychosocial treatment program, which has been described in detail elsewhere (10), involved weekly individual therapy as well as involvement with the family or significant others. As a complement to both medication strategies, individual therapy was aimed at establishing a close interpersonal bond between the schizophrenic patient and the clinician. This bond was used over time for purposes of gathering information, offering support and encouragement, identifying the beginning of relapse, enhancing patient cooperation in medication changes at relapse, and otherwise helping the patient deal with the complex social demands that are so difficult for individuals with this illness. Attention to phenomenology and current stressors rather than insight-oriented exploration was the basis for the clinical relationship. An educational approach was also used to inform the patient, the family, and other caretakers regarding the nature and treatment of schizophrenia and to form a link between clinical caretakers and families so that joint therapeutic efforts could be established and coordinated (10, 24, 25). This work included developing a shared view of relapse phenomena, including helping patients and others to be aware of early warning signs (prodromal symptoms) such as dysphoric affect, insomnia, increased suspiciousness, or worsening of baseline symptoms (14, 19, 26).

Patients assigned to the targeted-medication group remained drug free until symptoms appeared that were suggestive of a prodromal phase of a psychotic episode; at that time a standard intervention routine was initiated. This routine called for the immediate administration of neuroleptic drugs at therapeutic doses. When the patient was restabilized, which in most instances was within a relatively brief time (4 to 6 weeks), medication was discontinued and the monitoring and intervention (as needed) process was repeated. Patients assigned to the continuous-medication group were subjected to the same monitoring and intervention process. For this group, dose levels were raised when prodromal symptoms appeared and lowered when restabilization occurred.

During the initial stabilization, drug-free, and experimental treatment phases of the study, most decompensations were successfully managed on an outpatient basis. Those patients who required inpatient treatment were admitted to their local hospital until they were again candidates for outpatient treatment. On discharge, they continued in experimental treatment at the clinic, provided they had been hospitalized for less than 6 months. Periods of hospitalization that occurred within the experimental treatment phase were considered as time in the study.

Assessment Measures

Case history and prognostic instruments completed during the stabilization period included a nonstandard brief psychiatric history and a prognostic scale developed by Strauss and Carpenter (27), the latter providing information that was used for randomization of patients to experimental treatment on the basis of chronicity. Diagnostic instruments included a modified version of the Present State Examination (PSE) (28), which considered psychopathology during past episodes and during the present off-medication condition, and the Research Diagnostic Criteria (RDC) (29). These instruments were also used to further verify the diagnosis of schizophrenia.

Assessment instruments included the Brief Psychiatric Rating Scale (BPRS) (30), the Global Assessment Scale (GAS) (31), the Level of Functioning Scale (32), and the Quality of Life Scale (33). These instruments were completed initially and at 6, 12, 18, and 24 months by an evaluator who was not a member of the treatment team and whose sole function during the experimental treatment phase was to make independent assessments of outcome. (During the 6-month assessment interviews, self-reports of being on medication did not compromise the blind. Reports of not being on medication were rarely volunteered and could have been indicative of noncompliance. The patients were not asked if medication was being prescribed for them.) In order to define each patient's symptom status for ongoing clinical purposes, including the determination of decompensation, the BPRS was completed weekly by the patient's primary therapist.

In addition to symptom and functioning ratings completed at 6-month intervals by the independent evaluator, outcome criteria of effectiveness included retention rate, number of decompensations, and frequency and duration of hospitalizations (patients were free to continue the study following hospitalization if they were hospitalized for less than 6 months). Assessment of the effectiveness of targeted medication also included medication information such as percent of time drug free and extent of dose reduction.

Formal reliability studies of the assessment instruments, conducted at several points during the course of the treatment evaluation program with patient sample sizes ranging from eight to 13, provided satisfactory evidence of rater comparability. Agreement between the ratings of the independent rater and other staff members tended to be high; the intraclass correlation (ICC) (34) for total scores was usually over 0.70 and generally within the mid 0.80 to low 0.90 range. Assessment instrument factor and subscale score agreement was equally high for most factors. The rare subscale ICCs that fell in the mid 0.50 to mid 0.60 range were usually explainable in terms of restricted range; subsequent percentage agreement analyses demonstrated consistent rating patterns.

TABLE 1. Equivalency of Neuroleptic Doses Used in Comparison of Targeted and Continuous Medication

| Drug | Doses Considered Equivalent at Each Level | | | |
	Low	Moderate	Moderately High	High
Fluphenazine decanoate				
Oral and intramuscular (mg/day)	≤22.5	25–47.5	50–62.5	≥65
Depot (cc/2 weeks)	0.9	1.0–1.9	2.0–2.5	2.6
Other drugs (mg/day)				
Haloperidol (oral and intramuscular)	≤5	6–20	21–49	≥50
Loxapine	≤30	31–50	51–100	≥101
Thioridazine	≤200	201–400	401–600	≥601
Molindone	≤30	31–75	76–150	≥151
Thiothixene	≤10	11–25	26–49	≥50
Fluphenazine hydrochloride (oral and intramuscular)	≤1	2–5	6–19	≥20
Mesoridazine	≤100	101–200	201–400	≥401
Trifluoperazine	≤10	11–20	21–29	≥30
Chlorpromazine	≤300	301–599	600–999	≥1000
Perphenazine	≤20	21–40	41–60	≥61

Statistical Analyses

The major analyses used to determine treatment effects were analysis of variance and analysis of covariance (ANCOVA); ANCOVA was used for those evaluations for which available baseline information was used to control for initial level. A life table analysis was performed to examine time to first hospitalization. Hospitalization data were examined within successive 6-month periods over the 2 years of treatment. Psychiatric rating scale data were examined separately for years 1 and 2. To examine change over time as a function of treatment group, repeated measures analyses were used in additional analyses involving patients who completed the full 2-year experimental treatment course.

Because a variety of neuroleptics were administered to the patients, dose levels, categorized as none, low, moderate, moderately high, and high and scored from 0 to 4, were determined by using specific cutoff points for each drug. Presented in table 1, the equivalence levels used for neuroleptics involved in this study reflect a consensus of opinion of experts in psychopharmacological research (N.R. Schooler, personal communication). For each patient, the actual drug dose for each day was transformed to the 5-point scale (from 0 to 4) of dose level; averages over the course of treatment were determined on this measure. We felt that using this approach was more clinically relevant than using the traditional "chlorpromazine equivalents," especially those involving the conversion of depot neuroleptics (although routine procedures called for the administration of oral medication, depot medication was occasionally prescribed).

TABLE 2. Demographic Characteristics of Schizophrenic Outpatients Given Targeted or Continuous Medication for 2 Years

Characteristic	Targeted (N=57)	Continuous (N=59)
Sex		
Men		
Number	34	37
Percent	59.6	62.7
Women		
Number	23	22
Percent	40.4	37.3
Race		
Black		
Number	36	37
Percent	63.2	62.7
White		
Number	21	22
Percent	36.8	37.3
Education (years)		
Mean	12.5	12.6
SD	2.1	2.3
Age at admission (years)		
Mean	28.4	27.8
SD	5.6	5.8
Duration of illness (years)		
Mean	5.5	4.6
SD	4.7	3.8
Strauss-Carpenter Prognostic Scale score[a]		
Mean	2.0	2.0
SD	0.3	0.3

[a]0=poor; 4=excellent.

RESULTS

Patients

Of 116 patients who completed the requirements of the drug-free phase, 57 were randomly assigned to targeted treatment and 59 to continuous treatment. The demographic characteristics of these patients are presented in table 2. Because random assignment was within sex, race, and prognosis categories, the two groups were quite similar in these aspects. In fact, the two groups did not differ significantly on any of the measures presented in table 2. Approximately three-fifths of the entire group of patients were men, and three-fifths were black. The average prognostic score of 2.0 for the sample, midway between 0 (poor prognosis) and 4 (excellent prognosis), indicated only fair prognosis. The average age of the sample at admission to the program was approximately 28 years (range= 18–43). Most of the patients had graduated from high school, and many had attended at least one year of college. The average duration of illness of approximately 6 years for the sample indicated a generally chronic course of illness.

Consistent with the characteristics of the earlier sample in our ongoing program of research, approximately half of the patients were diagnosed as having paranoid schizophrenia and the remaining diagnoses were fairly evenly distributed between RDC undifferentiated schizophrenia and schizoaffective disorder,

mainly schizophrenic. The mean scores for the GAS fell in the range of 41 to 50, reflecting serious symptoms and/or impairment in functioning that obviously required treatment. The mean Level of Functioning Scale total score generally reflected little to no employment, and social functioning scores indicated limited interpersonal involvement.

Retention in the Study

At the end of 1 year, 40 (70%) of the 57 targeted-medication patients and 52 (88%) of the 59 continuous-medication patients were still involved in the treatment program. Twenty-eight (49%) of the targeted-medication patients and 48 (81%) of the continuous-medication patients completed the prescribed 2-year treatment course. (Six targeted-medication and four continuous-medication subjects who were in treatment for at least 1 year and still in treatment at the conclusion of the study were considered among the completers.) The differential 2-year completion rate in favor of continuous treatment was significant (χ^2= 11.94, df=1, p<0.001). Reflecting this differential retention rate, the mean±SD length of treatment for the targeted-medication group was 15.8±8.3 months, and that for the continuous-medication group was 20.5± 6.8 months (F=11.24, df=1, 108, p<0.001). Of the 29 targeted-medication patients who failed to complete treatment, 19 (33% of the targeted-medication sample) were considered to be treatment-related dropouts, mostly patients who refused to continue treatment. The remaining 10 patients (18%) dropped out of treatment for non-treatment-related reasons. Corresponding figures for the 11 continuous-medication patients who failed to complete treatment included eight treatment-related dropouts (14% of the continuous-medication sample) and three (5%) non-treatment-related dropouts.

To determine whether differential retention rates produced a biasing influence on other analyses of comparative effects, we examined the prognostic features of targeted-medication versus continuous-medication dropouts. Mean prognostic scale scores for dropouts from the two treatment groups were nearly identical. Also, there were no significant differences between the mean prognostic scores of dropouts versus completers for the entire sample and within each treatment group.

Dose Levels

Three measures of daily drug dose levels were examined: the average daily dose levels over the entire study, including days hospitalized (for each day in the hospital, it was assumed that a moderately high dose level, i.e., a score of 3, would be administered); the average daily dose level for the entire period of outpatient treatment, including days with and days without medication; and the average daily dose level while receiving medication in the outpatient clinic. Resulting data for these three measures are presented in table 3.

TABLE 3. Average Neuroleptic Dose Levels of Schizophrenic Outpatients Given Targeted or Continuous Medication for 2 Years

| Period | Average Dose Level[a] | | | | ANOVA | | |
| | Targeted (N=57) | | Continuous (N=59) | | | | |
	Mean	SD	Mean	SD	F	df	p
Entire study	1.22	0.79	1.79	0.81	14.48	1, 114	0.0002
All days as outpatient	1.02	0.75	1.73	0.84	23.46	1, 114	0.0000
All days of drug treatment, except during hospitalizations	2.18	0.77	2.01	0.71	1.56	1, 107	0.21

[a]0=no drug, 1=low dose, 2=moderate dose, 3=moderately high dose, 4=high dose.

That a substantial reduction in drug dose level was accomplished by targeted administration of medicine is evident, even when one assumes continuous administration of moderately heavy doses during hospitalizations (see table 3). Considering outpatient treatment only, including the entire period (days with plus days without medication), the reduction in dose level associated with targeted treatment could be roughly equated to a change from a moderate to a low dose level of neuroleptic medication. The extent of the dose reduction is most meaningfully illustrated by the comparative results of the respective high- and low-potency drugs haloperidol and chlorpromazine. The mean daily dose of haloperidol for targeted-medication patients was 4.4 ± 1.1 mg, whereas that for continuous-medication patients was 11.8 ± 4.4 mg. The mean daily dose of chlorpromazine for targeted-medication patients was 173 ± 69 mg, whereas that for continuous-medication patients was 433 ± 46 mg.

Considering only those periods of time when medication was administered to patients in the outpatient program, we found that the dose level for targeted-medication patients was slightly but not significantly higher than that for continuous-medication patients. Obviously, the reduction in dose level achieved with the targeted-medication strategy was through a reduction in the number of days medication was administered rather than the dose prescribed during targeted-medication intervention. Consistent with this interpretation, the 57 targeted-medication patients were drug free 48% of the time, and the 59 continuous-medication patients were drug free for approximately 10% of the time.

Decompensations

During the comparative trial, worsening in a patient's functioning and/or symptoms, as judged jointly by the primary therapist and the research psychiatrist, was noted in the patient's record. Such decompensations, which in most instances were not serious enough to warrant hospitalization, appear to be similar to the "minor exacerbations" described by Marder et al. (7) in their evaluation of the effectiveness of reduced medication with schizophrenic outpatients. In the present study, decompensations invariably prompted clinical intervention by the outpatient staff, usually in the form of a change in medication dose. The mean±SD numbers of decompensations experienced by targeted-medication and continuous-medication patients were 4.21 ± 3.70 and 2.75 ± 2.56, respectively (F=6.08, df=1, 114, p=0.015). Controlling for time in the study (since, on average, targeted-medication patients were not in the study as long as continuous-medication patients) yielded a yearly decompensation rate of 3.18 for the targeted-medication strategy and 1.60 for continuous treatment.

Hospitalizations

Thirty (53%) of the targeted-medication patients and 21 (36%) of the continuous-medication patients were hospitalized during the course of their treatment (χ^2=2.76, df=1, p=0.097). The average numbers of hospitalizations experienced by these 30 and 21 patients were 2.0 and 1.7, respectively, yielding a total of 60 hospitalizations for the targeted-medication group and 36 hospitalizations for the continuous-medication group. The F ratio for the resulting mean difference of 1.1 ± 1.1 versus 0.6 ± 0.9 hospitalizations per patient for the targeted-medication and continuous-medication groups, respectively, was 4.88 (df=1, 99, p=0.030).

Life table analysis results yielding comparative information on how long patients in the two groups remained out of the hospital before their first hospitalization are presented in figure 1.

The difference in survival rates for patients in the two groups with respect to avoidance of hospitalization was significant (generalized Wilcoxon statistic= 6.38, p=0.012); the relatively favorable outcome for continuous treatment was effected within the first year of the study. Although both targeted-medication and continuous-medication patients were more likely to be hospitalized for the first time during year 1 of the study, the rate at which targeted-medication patients were hospitalized during this period was significantly greater. There was little to no differentiation between the two groups during year 2; the patients who were not hospitalized during year 1 in both groups generally demonstrated a continuing resistance to hospitalization.

The mean number and duration of all hospitalizations (including rehospitalizations) for the two treatment groups within successive 6-month periods are

FIGURE 1. Rates of Nonhospitalization Among Schizophrenic Outpatients Given Targeted or Continuous Medication for 2 Years
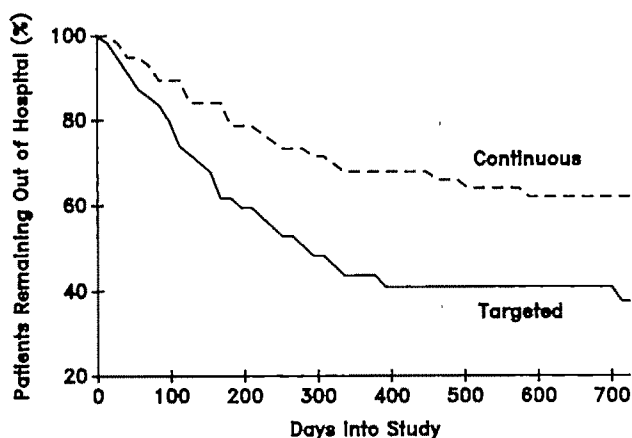
presented in table 4. The highest rate of hospitalization for both groups was in the first 6-month period. Although the rate for the targeted-medication group was double that for the continuous-medication group during the first period, the difference between groups did not quite reach significance. A differential rate in favor of the continuous-medication group continued into the second 6-month period, and at this time the difference was significant. Although there was less of a differential rate of hospitalization in the remaining 6-month periods, particularly the 13–18-month period, the direction of the differences continued to favor continuous over targeted medication. The results for mean duration of hospitalization also tended to favor continuous treatment for all but the last 6-month period.

Clinical Course

Level of Functioning Scale. The principal outcome measure used in the present study was the Level of Functioning Scale, completed by the independent rater at each of the 6-month evaluation points. Results of ANCOVA of Level of Functioning Scale ratings of the behavior and symptoms of patients during the immediately preceding 6 months for years 1 and 2 are presented in table 5.

For year 1, Level of Functioning Scale results for the two groups were essentially the same; the mean total scores adjusted for baseline differences were almost identical. On average, the degree of impairment of both groups was moderate. Only a small percentage of the patients had been hospitalized during the preceding 6-month period, generally not for an extended period of time. Mean social ratings indicated more than monthly but less than weekly social contacts and the maintenance of one or two moderately close relationships. Occupational ratings indicated some useful work (in many instances "around the house" or in sheltered workshops) but less than half-time occupation; competence was judged to be low on average.

Year 2 Level of Functioning Scale results indicate a clear differentiation between the two groups in terms of employment. For the 19–24-month period, continuous-medication patients, on average, were employed slightly more than half-time, and their competence rating approached the moderate range. By comparison, targeted-medication patients were significantly less employed and less competent. This difference in outcome is largely the reason for the significant difference in Level of Functioning Scale total score noted in table 5, although the mean score differences for all but one Level of Functioning Scale item directionally favored continuous over targeted treatment.

Other psychiatric rating scales. ANCOVAs were also performed on the remaining psychiatric ratings completed by the independent evaluator at 1 and 2 years. For these analyses, involving the BPRS and Quality of Life Scale total and factor scores and the GAS score, baseline assessments served as the covariate. The number of subjects for the 1-year analyses ranged from 25 to 29 for targeted treatment and from 39 to 46 for continuous treatment. For the 2-year analyses, the respective ranges for number of subjects were 16 to 20 and 24 to 40. Although the direction of the mean differences that were found generally favored continuous treatment, none of the differences was statistically significant; the p values for the covariance F ratios were uniformly above the level of 0.05.

Results for the entire sample evaluated at the end of 2 years generally revealed little change in overall psychiatric status from that observed at baseline. For the group as a whole, Quality of Life Scale, Level of Functioning Scale, and GAS scores were still indicative of an occasional display of moderate signs and symptoms, moderate impairment of both social and occupational functioning, and a continuing need for treatment, which infrequently involved hospitalization. When they did occur, hospitalizations were usually brief.

Graphic illustration of the targeted approach. To clarify what the targeted procedure entails in the way of dose manipulation, we present a "good" targeted-medication patient in figure 2. The patient chosen for illustration had a favorable outcome with the targeted procedure and displayed sufficient interaction between clinical status and medication level to be particularly informative. This white, male patient was drug free 60% of the time over the 2-year treatment period. His average daily drug dose level was 0.8, which is less than 300 mg chlorpromazine equivalents. Although he experienced six decompensations over the 2-year period, all were satisfactorily handled on an outpatient basis. Figure 2 shows that each decompensation was associated with an increase in medication level. For the first decompensation, the increase in medication was to a relatively high level for a fairly extended period (7–8 weeks). Thereafter, increases were more moderate and were in effect for shorter periods. Decompensations in this case were principally characterized by increased hostile suspiciousness and/or anxious de-

TABLE 4. Number and Duration of Hospitalizations for Schizophrenic Outpatients Given Targeted or Continuous Medication for 2 Years

Hospitalization Variable and Period	Targeted (N=57)		Continuous (N=59)		ANOVA		
	Mean	SD	Mean	SD	F	df	p
Number of hospitalizations							
Period							
0–6 months	0.46	0.71	0.23	0.50	3.65	1, 101	0.06
7–12 months	0.41	0.65	0.15	0.49	5.11	1, 83	0.03
13–18 months	0.21	0.52	0.19	0.49	0.01	1, 50	0.90
19–24 months	0.25	0.44	0.08	0.28	3.24	1, 40	0.08
Duration of hospitalizations (days)							
Period							
0–6 months	13.6	31.0	5.7	18.4	2.80	1, 101	0.10
7–12 months	18.0	34.0	5.3	15.6	5.44	1, 83	0.02
13–18 months	14.2	27.8	4.7	13.0	3.90	1, 50	0.05
19–24 months	5.6	13.0	6.6	27.7	0.03	1, 40	0.86

TABLE 5. ANCOVA Adjusted Mean Scores on the Level of Functioning Scale for Patients Given Targeted or Continuous Medication for 2 Years[a]

Scale Item	Year 1			Year 2		
	Targeted (N=29)	Continuous (N=46)	F (df=1, 72)	Targeted (N=21)	Continuous (N=36)	F (df=1, 54)
	Mean	Mean		Mean	Mean	
Duration of hospitalization	3.48	3.69	1.50	3.69	3.65	0.02
Frequency of social contacts	2.66	2.50	0.33	2.07	2.46	1.46
Quality of social relationships	2.20	2.14	0.06	1.80	2.17	1.96
Extent of employment	1.54	1.70	0.35	1.14	2.20	9.29[b]
Quality of employment	1.27	1.59	1.88	0.96	1.77	9.66[b]
Symptoms	1.89	1.98	0.22	1.87	2.16	1.19
Ability to meet basic needs	3.72	3.91	2.14	3.71	4.00	3.39
Fullness of life	2.25	2.14	0.31	2.13	2.42	2.33
Degree of impairment	2.03	2.02	0.00	1.83	2.15	2.31
Total score	21.10	21.61	0.16	19.33	22.92	6.70[b]

[a]Year 1 evaluations covered months 7–12, and year 2 evaluations covered months 19–24. Level of Functioning Scale scores range from 1 to 4; higher scores indicate better functioning.
[b]p<0.01.

FIGURE 2. Drug Dose Levels and Decompensation in a Schizophrenic Outpatient With a Favorable Outcome Who Was Given Targeted Medication for 2 Years
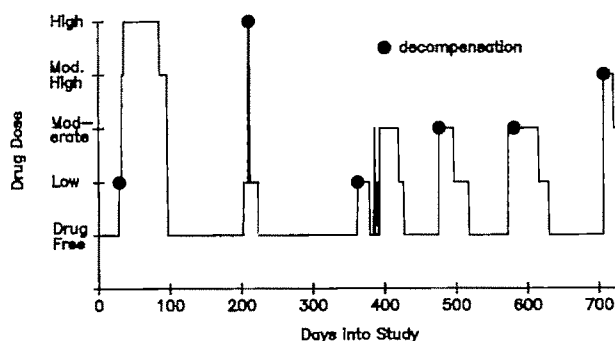
pression, as defined and measured by use of the BPRS. Determined on the basis of average BPRS scores, thought disturbance, a psychosis factor involving conceptual disorganization, hallucinations, and unusual thoughts, was rated as moderate at the first decompensation (which possibly explains the higher dose level at this point) and as mild during subsequent decompensations. The average BPRS total score (the possible range is 18 to 126) was 22 during stable periods. During periods of decompensation, the average BPRS score was 36, and at no time was it higher than 45.

DISCUSSION

As demonstrated in our previous research (12), the targeted-medication approach resulted in a substantial reduction in the use of medication in a large proportion of patients, which has a presumptive bearing on tardive dyskinesia. Although the extent to which the targeted-medication approach reduced the incidence of tardive dyskinesia has yet to be fully determined (these results will be reported in a separate paper), support for the hypothesis that reduction of medication has a beneficial effect on dyskinesia comes from the finding of Kane et al. (6) that there were significantly fewer early signs of tardive dyskinesia in a group of patients receiving low neuroleptic doses than in a group receiving standard doses at 1 year. Also, Jolley et al. (13)

reported a trend indicating both reduced total neuroleptic dose and lower prevalence of tardive dyskinesia in targeted-medication patients after 1 year of treatment compared with continuous-medication control subjects.

In both this and our previous study, targeted administration of medication was associated with more frequent hospitalizations and a lower retention rate. The present findings of the superiority of continuous over targeted medication with respect to Level of Functioning Scale ratings of extent and quality of employment are noteworthy. It is apparent that in our unselected sample targeted medication was generally not beneficial with regard to work functioning. It is likely that the significantly higher rates of both hospitalization and decompensation, which tended to disrupt long-term stable employment, made an important contribution to the more impaired work functioning of some patients in the targeted-medication group.

In summarizing our experiences with the targeted approach, we are reminded of Mark Twain's evaluation of Wagner's music as being better than it sounds. Given the unselected nature of the present study sample, targeted medication is conceivably better than it appears. To enable broader generalization of study results, chronically ill outpatients typical of those seen in public sector clinics were assigned to treatment unselected for "good candidate" status for drug reduction. Also, patients remained in their assigned treatment group regardless of medication experience or clinical exacerbation during abrupt drug discontinuation. Although this allows broader generalization, it understates the efficacy of targeted drug therapy in more suitable candidates.

In applying the targeted-medication approach, the clinician could select what he or she initially considers a good case for medication reduction and quickly revert to one of several continuous drug strategies should targeted treatment prove ineffective. Thus, long-term targeted medication would be reserved for successful patients, for whom the extent of drug reduction would be considerable. To appreciate targeted medication's niche in the clinician's armamentarium requires consideration of the relative benefits of standard and reduced-medication approaches.

That continuous treatment with standard doses of neuroleptics diminishes the severity of psychotic symptoms and has a prophylactic action with respect to relapse are generally recognized benefits. Problems associated with this type of treatment, however, include 1) the development of untoward side effects, most notably tardive dyskinesia, in a substantial number of patients, 2) the postulated undesirable interaction between neuroleptics and the negative symptoms of schizophrenia during periods of clinical stability, and 3) the noncompliance of patients who refuse to take daily medication on a long-term basis (15). Also, anecdotal reports and findings from long-term follow-up studies of both patients who do well while not receiving any medication and patients who do poorly while

receiving prolonged drug treatment at substantial dose levels define subgroups for whom standard, continuous drug treatment may have an undesirable risk-benefit profile (20, 21). Conducted in Europe, these long-term studies also document the deintensification of psychosis with aging, thus identifying a phase in which the benefits of neuroleptics may decrease as the risks increase.

There is no doubt that untreated schizophrenia has dire consequences; accepting moderate risks may therefore be warranted if effective treatment can be offered. Continuously administered medication with standard doses is frequently necessary. For those patients for whom this approach is infeasible, not indicated, or problematic, the question is no longer one of drug treatment versus nonpharmacological treatment but whether substantial reduction in medication can be achieved without unacceptable risk. Several considerations support the feasibility of dose reduction approaches in the majority of treatment-responsive patients. For selected patients, such approaches are especially appropriate. Some patients never display an episodically recurrent condition, and others apparently pass through an episodic phase and reach a plateau of clinical stability as their disease progresses. In these circumstances, prophylaxis is not required (20, 21, 35, 36).

Clinical application of reduced medication approaches is now supported by mounting evidence from controlled trials of continuous low-dose drug therapy (5, 7, 8, 37). Results of these studies suggest that dose reduction can lead to a lessening of adverse effects and to improvement in some measures of well-being and in instrumental and interpersonal role performance (8, 38). A higher risk of psychotic exacerbation associated with this type of drug reduction requires that patients be observed carefully and that medication be increased on a temporary basis when indicated.

Like the continuous low-dose strategy, the targeted-medication approach is a strategy that calls for flexible, observant clinical management. The strategy is useful only for patients judged to have a psychotic illness that is responsive to neuroleptic treatment. It is particularly effective in patients who maintain insight early in relapse and can actively collaborate in treatment (26). Also, it is an alternative treatment for the patient who will not comply with continuous prophylactic medication.

Understandably, prophylactic maneuvers associated with the intermittent treatment strategy are more demanding of the time and energy of clinical personnel than those associated with conventional continuous drug treatment. In their study of selected patients, however, Jolley et al. (13) used a psychoeducational-psychosocial approach that was less intense than ours and concluded that the additional monitoring and medically supportive treatment required by intermittent administration of medication were not so great as to preclude the use of the targeted-medication strategy in the normal clinical setting.

The work of Jeste et al. (39) raised the concern that repeated interruptions of medication would be associated with a greater risk of persistent tardive dyskinesia even though patients who had had the greater number of drug interruptions in their retrospective study had been receiving treatment longer and had received higher accumulated doses of neuroleptics. Evidence to date from our prospective controlled study and from that of Jolley et al. (13) does not support the hypothesis that an intermittent approach is more conducive to dyskinesia than a continuous drug approach. Since the questions of incidence and persistence have not been sufficiently addressed, however, more information on this issue is needed before definite conclusions can be reached.

An additional concern has to do with the need to avoid a marked or too rapid increase in dose in the treatment of decompensation, particularly one involving an agitated patient, so as not to enhance the risk of neuroleptic malignant syndrome (40).

Advantages of the targeted-medication approach are that it provides a mechanism for pharmacological research requiring drug-free intervals; assures less exposure to neuroleptic drugs in long-term clinical monitoring; provides an alternative treatment for patients who are not compliant with continuous drug administration and for those who are at low risk for relapse; allows a conservative extension of neuroleptic treatment to psychosis not classified as schizophrenia; and, in a given case, provides the clinician with an additional neuroleptic treatment strategy in individualizing treatment planning.

We and others are in the process of identifying the type of patient for whom the targeted-medication approach is a viable alternative not associated with an unacceptable level of risk. Our experience with the drug-free period (41) indicates that, along with other screening devices, such a procedure may provide useful information on the selection of candidates for the targeted-medication approach. Our impression is that the most suitable candidates for targeted treatment are those individuals who demonstrate an initial ability to remain drug free for a brief trial interval (at least 4 weeks), who are cooperative and insightful regarding prodromes, who do not relapse precipitously, who do not have a history of physical assaultiveness, and who have a social network allowing supportive involvement of a significant other. Further information on this and other relevant issues will be forthcoming from the five-center National Institute of Mental Health collaborative study involving a direct comparison of targeted and continuous low- and standard-dose strategies (42).

In clinical practice, the pharmacological treatment strategy that one chooses for a particular patient may vary over time. Rather than competitors for general applicability, these strategies should be thought of as treatment alternatives that are variously applicable over the course of the illness. The heterogeneity of schizophrenia implies far more variability in treatment requirements, including type and dose of medication,

than has generally been reflected in treatment recommendations. In any given case, there should be discrete, individualized pharmacotherapeutic decision making in which adjustments in drug administration parallel shifts in benefits and risks. The targeted-medication strategy is an alternative that warrants consideration within this applications framework.

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Neuroleptic Malignant Syndrome in 12 of 9,792 Chinese Inpatients Exposed to Neuroleptics: A Prospective Study

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In a prospective study of an estimated 9,792 inpatients treated with neuroleptic medication at a large Chinese psychiatric hospital, 12 patients developed neuroleptic malignant syndrome. The estimated prevalence of neuroleptic malignant syndrome in these psychiatric inpatients was 1.23/1,000 (95% confidence interval=0.63/1,000 to 2.14/1,000). Unlike other investigators, the authors found that young adulthood, nonschizophrenic illness, oral high-potency neuroleptics, and concurrent use of lithium were not important risk factors for neuroleptic malignant syndrome. However, depot fluphenazine decanoate, particularly if used without an antiparkinsonian agent, was a risk factor.

(Am J Psychiatry 1990; 147:1149–1155)

N euroleptic malignant syndrome is a serious complication of neuroleptic therapy that has received increasing attention over the last decade. To date, more than 160 cases have been reported in the world literature (1). Almost all of the available reports are retrospective case reports that provide little or no information about the populations from which the cases were drawn. It is thus difficult to confirm the importance of the many hypothesized risk factors for neuroleptic malignant syndrome: young adulthood, male sex, nonschizophrenic illness, high-potency drugs, and concurrent medical illness (2). In this paper we report on a series of 12 inpatients with neuroleptic malignant syndrome who were prospectively collected over 7 years from a large Chinese psychiatric hospital and compare them to a randomly selected control group of 102 inpatients identified retrospectively who were ex-

posed to neuroleptics but did not develop neuroleptic malignant syndrome.

METHOD

All inpatients at the 700-bed Fang Cun hospital in Guangzhou (Canton) who were treated with neuroleptic medication from Jan. 1, 1980, to Dec. 31, 1986, were potential subjects. Clinicians in the hospital were required by hospital policy to report any patient receiving neuroleptic medication who developed a fever in combination with severe extrapyramidal symptoms. To rule out neuroleptic-induced encephalitis and other physical causes for the symptoms, each of these patients was given a thorough physical examination, appropriate laboratory tests (including liver and kidney function tests), chest X-ray, and—if needed—lumbar puncture. If none was found, the patient was diagnosed as having neuroleptic malignant syndrome. A total of 12 episodes of neuroleptic malignant syndrome were identified in 12 separate patients over the 7-year period (none of the patients had multiple episodes). Two of the patients (patients 5 and 8 in table 1) each had a diagnosis of catatonic schizophrenia, but catatonia was ruled out as a cause of the symptoms because the patients' catatonic symptoms had resolved long before the onset of the symptoms of neuroleptic malignant syndrome.

A retrospective control group was generated by randomly selecting 15 inpatient episodes (hereafter "inpatients") from each of the 7 years of the study. Of the 105 inpatients selected, the 102 patients (97.14%, 95% confidence interval=91.86%–99.41%) who used neuroleptics at some point during their hospital stays constituted the control group. Thus, it was estimated that 9,792 (97.14%) of the 10,080 patients over the 7 years of the study used neuroleptics. The proportions of specific characteristics and drug exposures in the control group were used to estimate the frequency of exposure to these potential risk factors in the 9,792 inpatients, i.e., the denominator for each risk factor. The number of patients who had each risk factor at the onset of neuroleptic malignant syndrome symptoms

TABLE 1. Characteristics of Neuroleptic Malignant Syndrome in 12 Chinese Patients[a]

Patient	Age (years)	Sex	Duration of Illness	Neuroleptic[b] and Dose	Duration of Neuroleptic Treatment at Onset of Symptoms (days)	Temperature (°C)	Parkinsonian Signs	WBC (cells/mm³)
1	20	M	3 months[c]	Depot fluphenazine, 25 mg/week; chlorpromazine, 350 mg/day	26	38.9	Hypertonic extremities, sialorrhea	11,500
2	41	F	14 years	Depot fluphenazine, 75 mg/week; haloperidol, 66 mg/day	64	38.3	Hypertonic extremities, oculomotor paralysis	20,100
3	38	F	7 years	Perphenazine, 46 mg/day; trihexyphenidyl, 6 mg/day	59	40.3	Lead-pipe rigidity, akinesia, dysphonia	20,400
4	21	F	4 years	Lithium, 1.4 g/day; haloperidol, 15 mg/day; trihexyphenidyl, 6 mg/day	2	37.6	Hypertonia, sialorrhea, dysphagia	10,200
5	28	F	8 years	Perphenazine, 6 mg/day	4	39.5	Hypertonia	8,900
6	29	M	7 years	Depot fluphenazine, 25 mg/week; chlorpromazine, 350 mg/day	42	39.4	Hypertonia, akinesia	15,800
7	29	M	7 years	Depot fluphenazine, 50 mg/week; chlorpromazine, 300 mg/day	27	39.0	Hypertonic extremities	14,500
8	34	M	13 years	Perphenazine, 30 mg/day; sulpiride, 400 mg/day; trihexyphenidyl, 6 mg/day	27	37.5	Hypertonic extremities, sialorrhea, dysphagia	18,500
9	29	M	2 years	Depot fluphenazine, 25 mg/week; perphenazine, 28 mg/day; chlorpromazine, 450 mg/day; trihexyphenidyl, 6 mg/day	7	40.0	Hypertonia, dyskinesia	14,000
10	33	M	8 years	Depot fluphenazine, 100 mg/week; clozapine, 300 mg/day; trihexyphenidyl, 6 mg/day	83	42.0	Hypertonia, dysphagia	23,000
11	44	F	22 years	Haloperidol, 55 mg/day	2	38.1	Hypertonia, dysphagia	—
12	26	M	4 years	Depot fluphenazine, 50 mg biweekly; haloperidol, 30 mg/day	14	37.5	Hypertonia, sialorrhea	—

[a]Patient 4 had a diagnosis of bipolar disorder, manic; the other patients each had a diagnosis of schizophrenia.
[b]Fluphenazine=fluphenazine decanoate.
[c]Chinese diagnostic criteria for schizophrenia (4) require only 3 months of symptoms.

(the numerator) was then used to calculate rates of neuroleptic malignant syndrome for each risk factor. We compared the neuroleptic malignant syndrome group and the control group with t tests, estimated confidence limits for rates by means of an exact method that uses the relationship between the F distribution and the binomial distribution (3), and compared rates of neuroleptic malignant syndrome for different characteristics by means of the binomial test (3). All p values reported are for two-tailed tests.

RESULTS

Characteristics of the 12 patients with neuroleptic malignant syndrome are presented in table 1. Most of these patients were under age 40, and all but one had a diagnosis of schizophrenia according to the Chinese Medical Association's diagnostic criteria (4). All of them were receiving high-potency neuroleptics at the time they developed neuroleptic malignant syndrome, seven (58%) were using depot fluphenazine decanoate, and eight (67%) were using more than one neuroleptic. The duration of continuous neuroleptic treatment at the onset of symptoms was 2–83 days (mean± SD=29.8±27.0 days). Each of the patients had a temperature of 37.5 °C or higher, extrapyramidal signs (such as muscular rigidity, sialorrhea, or dysphagia), and autonomic signs (such as hypertension, tachycardia, tachypnea, diaphoresis, or urinary incontinence). The WBC was higher than 15,000 cells/mm³ in five of the 10 patients (50%) for whom WBCs were available. Nine patients (75%) had some disturbance of consciousness.

TABLE 1 (continued)

Peak Autonomic Dysfunction			
Blood Pressure (systolic/ diastolic) (mm Hg)	Pulse (beats/min)	Other Autonomic Dysfunction	Other Symptoms
156/120	—	Diaphoresis, urinary incontinence	Stupor
150/110	—	Urinary incontinence	Stupor
150/110	130	Diaphoresis, respiration=30 breaths/min	Clouded consciousness
—	100	Diaphoresis	—
—	120	Diaphoresis	Somnolence
110/80	160	Diaphoresis, respiration=40 breaths/min	Clouded consciousness, creatine phosphokinase=2370 U/ml
130/90	120	Diaphoresis, urinary incontinence	—
—	120	—	—
150/100	138	Diaphoresis	Clouded consciousness
90/60	140	Urinary incontinence, respiration=30 breaths/min	Clouded consciousness
150/100	120	Diaphoresis	Somnolence
—	100	—	Clouded consciousness

TABLE 2. Treatment of 12 Chinese Patients With Neuroleptic Malignant Syndrome

Patient	Treatment	Duration of Symptoms (days)
1	Stopped neuroleptics; administered trihexyphenidyl and scopolamine	10
2	Stopped neuroleptics; treated symptoms	4
3	Stopped neuroleptics; administered bromocriptine, 7.5 mg/day, and orphenadrine, 15 mg/day	21
4	Stopped neuroleptics; administered trihexyphenidyl	4
5	Stopped neuroleptics; administered trihexyphenidyl, scopolamine, and promethazine	10
6	Continued neuroleptics at same doses; added bromocriptine, 30 mg/day, and dexamethasone	37
7	Continued neuroleptics at same doses; added trihexyphenidyl and scopolamine	30
8	Reduced dose of neuroleptics; added scopolamine	14
9	Stopped neuroleptics; administered trihexyphenidyl and symptomatic treatment	27
10	Continued neuroleptics at same doses; treated symptoms	4
11	Stopped neuroleptics; administered scopolamine and symptomatic treatment	4
12	Stopped neuroleptics; administered trihexyphenidyl, scopolamine, and dexamethasone	26

The treatment data are presented in table 2. Neuroleptic medication was stopped in eight cases, the dose was reduced in one case, and the dose was unchanged in three cases. Treatment also included different combinations of antiparkinsonian agents (nine cases), bromocriptine (two cases), dexamethasone (two cases), promethazine (one case), and symptomatic treatment (four cases). The duration of neuroleptic malignant syndrome symptoms was 4–37 days (mean±SD=15.9± 11.8 days). The mean duration of symptoms was almost twice as long for patients who used depot fluphenazine decanoate as the duration for those who did not, but this difference was not statistically significant (19.7±13.5 days versus 10.6±7.2 days; t=1.37, df= 10, p=0.20). All patients recovered fully with no sequelae. Neuroleptic malignant syndrome was specifically ruled out as a cause of death for all deaths at the

hospital over the 7 years of the study; thus, there were no deaths due to neuroleptic malignant syndrome among the 9,792 inpatients exposed to neuroleptics.

The mean±SD age of the 12 patients with neuroleptic malignant syndrome (31.0±7.4 years) was virtually identical to that of the 102 control subjects (31.4± 11.0 years). The mean±SD duration of illness for the neuroleptic malignant syndrome group was longer than that for the control group, but the difference was not statistically significant (8.0±5.9 years versus 6.2± 5.7 years; t=1.07, df=112, p=0.29). The mean±SD duration of the index hospitalization was significantly longer in the group with neuroleptic malignant syndrome (181±101 days versus 122±71 days; t=2.6, df=112, p<0.02).

The rates of neuroleptic malignant syndrome for patients with different characteristics and drug exposures are presented in table 3. The rate of neuroleptic malignant syndrome in inpatients exposed to neuroleptic medication was 1.23/1,000 (12/9,792); the exact 95% confidence interval for this rate is 0.63/1,000 to 2.14/ 1,000. Male patients had a higher rate of neuroleptic malignant syndrome than female patients, but because of the small number of cases this difference was not statistically significant (Z=0.36, p>0.05). The rates of

TABLE 3. Relation of Sex, Diagnosis, and Drug Treatment to Neuroleptic Malignant Syndrome in Chinese Inpatients Given Neuroleptics

| Variable | Patients With Neuroleptic Malignant Syndrome | | Control Patients | | All Inpatients | | |
| | | | | | | Estimated Rate of Neuroleptic Malignant Syndrome | |
	N	%	N	%	Estimated Number	Rate per 1,000	95% Confidence Interval[a]
Any neuroleptic medication	12	100.0	102	100.0	9,792	1.23	0.63–2.14
Sex							
Male	7	58.3	50	49.0	4,800	1.46	0.59–3.00
Female	5	41.7	52	51.0	4,992	1.00	0.33–2.33
Diagnosis							
Schizophrenia	11	91.7	90	88.2	8,640	1.27	0.64–2.28
All nonschizophrenia diagnoses	1	8.3	12	11.8	1,152	0.87	0.02–4.82
Affective disorders[b]	1	8.3	9	8.8	864	1.16	0.03–6.42
Drug treatment[c]							
Oral trifluoperazine	0	0.0	29	28.3	2,784	0.00	—
Oral haloperidol	4	33.3	27	26.5	2,592	1.54	0.42–3.95
Oral perphenazine	4	33.3	26	25.5	2,496	1.60	0.44–4.10
Oral chlorpromazine	4	33.3	70	68.6	6,720	0.60	0.16–1.52
Oral sulpiride	1	8.3	10	9.8	960	1.04	0.03–5.78
Oral clozapine	1	8.3	4	3.9	384	2.60	0.07–14.41
Any oral high-potency drug[d]	8	66.7	73	71.6	7,008	1.14	0.49–2.25
Any oral low-potency drug[e]	6	50.0	75	73.5	7,200	0.83	0.31–1.82
Depot fluphenazine decanoate	7	58.3	18	17.6	1,728	4.05	1.63–8.32
Depot fluphenazine without antiparkinsonian agent	5	41.7	4	3.9	384	13.02	4.24–30.09
Multiple neuroleptics concurrently	8	66.7	61	59.8	5,856	1.37	0.59–2.69
Lithium with neuroleptic	1	8.3	7	6.9	672	1.49	0.04–8.25

[a]Calculated by means of an exact method (3).
[b]Includes major depression, bipolar affective disorder, and schizoaffective disorder.
[c]Values for patients with neuroleptic malignant syndrome represent the number of patients who were using the drug at the onset of symptoms; values for control subjects and estimated values for all inpatients represent the number who used the drug at any time during the index admission.
[d]Includes trifluoperazine, haloperidol, perphenazine, oral fluphenazine decanoate (used by 10 control patients), pimozide (used by two control patients), and pipotiazine (used by two control patients).
[e]Includes chlorpromazine, sulpiride, clozapine, thioridazine (used by two control patients), and chlorprothixene (used by two control patients).

neuroleptic malignant syndrome in patients with affective disorders, in patients concurrently taking lithium, and in patients concurrently taking multiple neuroleptics were similar to the overall rate. Surprisingly, none of the 2,784 patients exposed to the most commonly used high-potency oral neuroleptic—trifluoperazine—developed neuroleptic malignant syndrome, and the rate in patients exposed to any oral high-potency neuroleptic was slightly lower than the overall rate. The rate in patients exposed to depot fluphenazine decanoate, however, was more than three times the overall rate (p<0.007, binomial test), and patients who used depot fluphenazine decanoate without concurrent antiparkinsonian agents had a rate of developing neuroleptic malignant syndrome 10 times as high as the overall rate (p<0.001, binomial test).

Comparing the drug doses received by the neuroleptic malignant syndrome patients at the onset of symptoms and the maximum doses received by the 102 control subjects during their hospitalization, we found no significant differences in the mean doses of individual neuroleptics or of the antiparkinsonian agent trihexyphenidyl (the main antiparkinsonian agent used in China). For patients using depot fluphenazine decano-

ate, the mean±SD doses of the neuroleptic malignant syndrome group and the control group were 44.5± 32.2 mg/week and 36.4±17.3 mg/week, respectively (t=0.84, df=23, p=0.41). The range of chlorpromazine-equivalent total doses of oral neuroleptics for the neuroleptic malignant syndrome patients was 300–1320 mg/day (mean±SD=599±326 mg/day); comparable data on the maximum total daily doses for the control group were not available.

DISCUSSION

Given that neuroleptic malignant syndrome is a relatively uncommon disorder and that a large number of Chinese patients use neuroleptic medication, Chinese researchers are in a position to make a major contribution to the growing body of world literature on this disorder. Since the publication in 1979 of a major Chinese review of neuroleptic side effects (5), including neuroleptic malignant syndrome, 27 cases have been reported in the two Chinese psychiatric journals that are available internationally (6–11). The current study adds 12 additional cases to the literature on neuroleptic malignant syndrome. It is a large series that was

prospectively collected, so it provides a stable estimate of the prevalence of neuroleptic malignant syndrome in hospitalized patients. To our knowledge, this is the only study that compares patients with neuroleptic malignant syndrome to a control group of subjects; it thus provides valuable new data on risk factors for the disorder.

Diagnostic and Therapeutic Issues

There is debate about whether neuroleptic malignant syndrome is a distinct diagnostic entity, with a unique etiology and pathogenesis, or simply an extreme form of extrapyramidal symptoms that is exacerbated by a variety of concurrent medical conditions (1, 12). To help focus this debate, Pope et al. (1) have proposed diagnostic criteria for neuroleptic malignant syndrome that can be applied prospectively or retrospectively. We retrospectively applied these criteria to our 12 cases and found that eight (patients 1–4, 6, 9–11) would be considered definite neuroleptic malignant syndrome, three (patients 5, 8, 12) would be considered probable, and one (patient 7) would not be considered neuroleptic malignant syndrome. The excluded patient had a temperature of 39.0 °C, hypertonic extremities, tachycardia, diaphoresis, urinary incontinence, and leukocytosis (WBC=14,500 cells/mm^3). The failure of Pope et al.'s criteria to include this case highlights the difficulty of establishing criteria that will encompass the many presentations of neuroleptic malignant syndrome. Our findings and those of authors who have reported milder variants of neuroleptic malignant syndrome (13–15) support the suggestion of Addonizio et al. (13) that neuroleptic malignant syndrome is a spectrum disorder.

There is also controversy about the treatment of neuroleptic malignant syndrome (2, 16, 17). If the cause is neuroleptic-induced dopamine blockade, then the dopamine agonist bromocriptine would be a rational treatment. There have been several reports of rapid resolution of the symptoms of neuroleptic malignant syndrome after bromocriptine administration (18–20). The two patients we treated with bromocriptine—one with 30 mg/day and one with 7.5 mg/day (a relatively low dose)—did not have spectacular recoveries; after 1 week other medication had to be used to treat their persistent muscular rigidity. Our results are also at odds with the estimated mortality rate of 20% to 30% (2). All of our 12 patients recovered fully, and none of the 9,792 inpatients who used neuroleptics died of neuroleptic malignant syndrome. Rosebush and Stewart (21), who recently reported on a large series of patients, also found that with early recognition and good supportive care neuroleptic malignant syndrome need not be fatal.

Prevalence

These cases were collected prospectively, so we are confident that we identified virtually all the patients that met our inclusion criteria of a medically unexplained fever and severe extrapyramidal symptoms. Moreover, the number of inpatients exposed to neuroleptics is large (N=9,792), so our estimated prevalence of 1.23 patients per 1,000 inpatients exposed to neuroleptics (0.12%) is fairly precise. Previous Western reports based on retrospective studies, which involved relatively small numbers of patients at risk, indicated much higher prevalences—2.4% (two of 82) (13) and 1.4% (seven of 483) (1)—and in one prospective study (22) the prevalence was 0.9% (six of 679). In larger studies from non-Western countries the prevalences were similar to the one found in this study: 0.2% (three of 1,500) (23) and 0.15% (six of 4,000) (24).

There are several possible explanations for this wide range in estimated prevalences: 1) the thoroughness of case ascertainment may vary greatly across studies, 2) diagnostic criteria differ, 3) the age, sex, diagnostic distribution, and medical condition of patients exposed to neuroleptics is different in different settings, and 4) the type of neuroleptic, dose, rate of dose change, and the frequency of concurrent use of neuroleptics and antiparkinsonian agents or lithium vary widely among different treatment settings. Unfortunately, the few reports including estimates of the prevalence of neuroleptic malignant syndrome did not provide data on the characteristics of the patients at risk or on the pattern of medication use in the treated population. Therefore, it is difficult to test hypotheses about the differences in reported prevalences of neuroleptic malignant syndrome.

There are some characteristics that distinguish our 9,792 patients from most Western samples and, thus, may be related to the low prevalence of neuroleptic malignant syndrome: 1) all the patients were of the Chinese Han racial group, 2) only 8.8% of the patients had affective disorder diagnoses (Chinese clinicians tend to overdiagnose schizophrenia [25, 26], so a higher proportion of the patients would have had affective disorder diagnoses if *DSM-III-R* criteria had been used) and only 6.9% of all the patients concurrently used lithium and a neuroleptic, 3) because of the relatively long hospital stays of patients in China (mean of 122 days for our control subjects), Chinese clinicians tend to increase oral doses of neuroleptics more slowly than Western clinicians and to use lower maximum doses of oral drugs, and 4) 79.6% of all the patients were concurrently using antiparkinsonian agents.

Risk Factors

In the absence of information about the populations from which patients with neuroleptic malignant syndrome are drawn, the importance of the many previously proposed risk factors is doubtful. In this study we determined the relative importance of potential risk factors by comparing the rates of neuroleptic malignant syndrome in persons exposed to these factors.

The computed rates are based on small numbers of cases, so interpreting differences in rates must be done cautiously, but our findings contrast sharply with those in previous reports. Neuroleptic malignant syndrome has been reported to be more common in young men (27), patients with nonschizophrenic illnesses (28), patients who are using high-potency drugs (29), and patients who concurrently receive neuroleptics and lithium (1). We did find a higher rate in men than in women, but young adulthood, nonschizophrenic illness, use of oral high-potency neuroleptics, and concurrent use of lithium did not appear to be important risk factors in our patients. Our study, however, had low power (because of the small number of patients with neuroleptic malignant syndrome) and may not have detected small differences in the rates of neuroleptic malignant syndrome between patients with different exposures.

The rate of neuroleptic malignant syndrome in patients exposed to depot fluphenazine decanoate was significantly higher than the overall rate, and the rate in patients who used depot fluphenazine without concurrent antiparkinsonian agents was extremely high. The importance of depot fluphenazine in our sample of inpatients may be related to the relatively high doses used.

Our data do not address some potential risk factors: patients with medical syndromes that may predispose to neuroleptic malignant syndrome were specifically excluded, the total duration of exposure to specific neuroleptics was not known, the rate of dose increases was not calculated, and the maximum total daily doses of neuroleptics for control patients using multiple oral medications were not available. We cannot, therefore, comment on the importance of these factors, in the development of neuroleptic malignant syndrome.

Since each patient with neuroleptic malignant syndrome has been exposed to multiple risk factors, there is considerable confounding of factors. Moreover, it is possible that particular combinations of factors—not individual factors—result in a high risk for neuroleptic malignant syndrome. Controlling confounders and assessing possible interaction effects by using multivariate analyses would help identify the most pertinent risk factors, but this type of analysis would require a much larger group of patients with neuroleptic malignant syndrome.

The relatively infrequent occurrence of neuroleptic malignant syndrome makes it difficult for any one researcher to systematically collect sufficient cases to test etiologic, diagnostic, or therapeutic hypotheses. Moreover, the symptomatic heterogeneity and frequent failure to exhaustively exclude medical causes in the published case reports seriously limit the validity of conclusions drawn by combining data across studies. The conundrums of neuroleptic malignant syndrome will remain unresolved until a uniform protocol for case ascertainment, data collection, and treatment is prospectively applied at a number of large psychiatric centers. We would be interested in collaborating with other researchers to organize such a multicenter study.

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Factors in the Development of Severe Forms of Tardive Dyskinesia

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The authors evaluated 558 patients for tardive dyskinesia. They found that the prevalence of tardive dyskinesia was 34%. There were no differences between men and women in prevalence of tardive dyskinesia. However, severe tardive dyskinesia was found to occur more in male patients 40 years old or younger and in female patients 71 years old or older. Patients with mild tardive dyskinesia received more neuroleptics than did patients with moderate and severe forms. However, patients with moderate tardive dyskinesia had significantly more drug-free periods in their drug histories than did patients with mild tardive dyskinesia.
(Am J Psychiatry 1990; 147:1156–1163)

S evere tardive dyskinesia has rarely been the focus of systematic studies. Data based on referred cases (not on prevalence studies) have been published (1, 2). Gimenez-Roldan et al. (1) reported on nine patients with tardive dystonia and 13 with tardive dyskinesia whom they saw in consultation in a neurology department. Similarly, Gardos et al. (2) reported on 19 patients with severe tardive dyskinesia whom they saw in their consultation department; they compared these 19 patients with 45 patients examined in their hospital who had mild tardive dyskinesia. Gardos and Cole (3) commented on the lack of cases of severe tardive dyskinesia, which may be the reason why patients with severe tardive dyskinesia are seldom discussed or presented in the literature. Although these patients may show grotesque movements associated with distress and functional impairment (4, 5), most of the reports in the literature consist of anecdotal descriptions rather than systematic studies of the factors leading to the development of the more severe forms of tardive dyskinesia.

Another difficulty in dealing with severe tardive dyskinesia has been the problem of the measurement of severity; criteria for severity have not been uniformly applied. Some authors (6) use the total score of a scale as their criterion of severity, others (2, 7) use the level of subjective and objective distress and degree of functional impairment as measures of severity, and still others (8) use the severity criterion of one body area. There are problems with classifying the severity of tardive dyskinesia according to the first two systems. If we use the total score criterion, patients exhibiting severe tardive dyskinesia in one body area may have a low total score and thus would not be considered as exhibiting severe tardive dyskinesia. In addition, using the criteria of distress and incapacitation as indicators of severity may not apply to all patients because patients with tardive dyskinesia may rarely complain of their movements (9). All these considerations led us to choose the severity criterion of one body area as a measure of severity.

Our aim in the present study was to identify demographic characteristics of patients with severe tardive dyskinesia in a large group of patients. In addition, we carried out an in-depth comparison of patients with severe, moderate, or mild tardive dyskinesia to identify treatment variables associated with severity of tardive dyskinesia.

METHOD

The study group consisted of 355 patients admitted to the chronic wards of our hospital, including the psychogeriatric inpatient units, and 203 outpatients attending the follow-up clinics of the hospital. The 558 patients included 263 men and 295 women. All of the patients were assessed during the year 1987 by using the Simpson Rating Scale (10). This scale measures tardive dyskinesia on a scale of 1–6 on which 1=no tardive dyskinesia and 6=severe tardive dyskinesia. A score of 3 (mild tardive dyskinesia) on the scale in one body area was sufficient for the diagnosis of tardive dyskinesia. Approximately 60% of the 558 patients had been assessed previously on several occasions (11, 12).

For the diagnosis of severe tardive dyskinesia, a

TABLE 1. Age of and Neuroleptic Use by 558 Psychiatric Patients With or Without Tardive Dyskinesia

Diagnosis and Sex	Age at Time of Study (years)		Duration of Neuroleptic Use (years)		Current Neuroleptic Dose (mg/day)[a]	
	Mean	SD	Mean	SD	Mean	SD
Tardive dyskinesia (N=191)						
Men (N=80)	60.8	14.2	22.4	8.3	538.8	571.3
Women (N=111)	68.7	10.3	22.9	8.7	299.5	491.8
Mild (N=91)						
Men (N=41)	64.4	11.0	24.2	7.8	559.6	541.0
Women (N=50)	66.5	9.8	25.6	7.0	382.4	597.1
Moderate (N=80)						
Men (N=32)	58.1	14.5	21.5	7.9	540.2	621.9
Women (N=48)	70.8	11.0	20.0	9.6	234.9	437.9
Severe (N=20)						
Men (N=7)	39.3	12.5	9.7	7.5	350.0	144.3
Women (N=13)	71.9	10.8	24.8	7.2	198.8	235.0
No tardive dyskinesia (N=367)						
Men (N=183)	52.9	14.6	20.1	9.4	749.1	921.8
Women (N=184)	59.2	15.8	22.1	9.3	647.5	846.6
Total (N=558)						
Men (N=263)	55.4	14.7	20.9	8.9	691.8	840.7
Women (N=295)	62.8	14.7	22.4	8.9	516.2	753.7

[a]There were significant differences between the men with and without tardive dyskinesia (t=2.25, df=234, p<0.03), between the women with and without tardive dyskinesia (t=4.47, df=293, p<0.0001), and between all of the men and all of the women (t=2.59, df=500, p<0.01).

score of 5 (moderately severe) or 6 (severe) in one body area was required. Thus, if severe tardive dyskinesia was present in one body area and other degrees of severity were present in other parts of the body or if severe tardive dyskinesia was present in only one body area, the patient was diagnosed as having severe tardive dyskinesia. Similarly, moderate tardive dyskinesia was diagnosed if the patient had a score of 4 in one body area, and mild tardive dyskinesia was diagnosed if the patient's score was 3. Approximately 60% of our patients with moderate and mild tardive dyskinesia had been assessed previously and were found to have stable tardive dyskinesia (13).

One of us (R.Y.) assessed the patients once. To be included in the study, a patient had to have received neuroleptics for at least 2 years. Diagnoses of schizophrenia and affective disorder were made according to DSM-III. The doses of neuroleptics were converted to chlorpromazine equivalents by using the Davis formula (14).

Following the identification of the patients with tardive dyskinesia, their files were reviewed for the following information: 1) age at onset of psychosis, 2) age at initiation of neuroleptic treatment, 3) total intake of psychotropic drugs, 4) diagnosis, 5) organic conditions, 6) drug-free periods, 7) when the movement disorder was first noted in the file.

Drug-free periods were defined as any interruption of neuroleptic administration either recommended by the physician or conducted by the patient (i.e., the patient refused treatment) and recorded in the patient's file. Only drug-free periods lasting for 3 months or more were considered.

To diagnose organic treatments or conditions, such as ECT and diabetes mellitus, we used the criteria of Simpson et al. (15). Only files that were complete from the first onset of psychosis to the present were included in this analysis.

RESULTS

The mean±SD age of the 558 patients was 59.2± 15.2 years. The 263 men were significantly younger than the 295 women (55.4±14.7 versus 62.8±14.7 years, t=5.93, df=556, p<0.001).

Prevalence of Tardive Dyskinesia

One hundred ninety-one (34%) of the 558 patients in our study were found to have tardive dyskinesia in one or more body areas. Eighty (30%) of the men and 111 (38%) of the women had the disorder. The difference in prevalence of tardive dyskinesia between men and women was not statistically significant (χ^2=2.995, df=1).

Thirty-two (12%) of the men and 48 (16%) of the women had moderate tardive dyskinesia. Seven (3%) of the men and 13 (4%) of the women had severe tardive dyskinesia. These differences were not statistically significant. As shown in table 1, men with severe tardive dyskinesia were younger and had a shorter duration of neuroleptic therapy than any of the other patients with or without tardive dyskinesia. Men and women without tardive dyskinesia had significantly higher mean current neuroleptic doses than men and women with tardive dyskinesia, and men with and without tardive dyskinesia had significantly higher mean current neuroleptic doses than women.

TABLE 2. Characteristics of 20 Patients With Severe Choreoathetoid Dyskinesia or Tardive Dystonia

Characteristic	Patients With Choreoathetoid Dyskinesia (N=11)	Patients With Tardive Dystonia (N=9)
Male-female ratio	0:11	7:2
Age (years)		
Mean	74.0	44.1
SD	7.3	16.8
Range	65–91	26–78
Simpson Rating Scale score[a]		
Mean	27.2	13.0
SD	13.8	7.9
Range	6–54	6–24
Current neuroleptic dose (mg/day)		
Mean	230.0	277.8
SD	243.0	190.6
Range	55–900	0–600
Time since first exposure to neuroleptic (years)		
Mean	14.9	7.1
SD	8.6	4.8
Range	5–30	1–14

[a]1=no tardive dyskinesia, 6=severe tardive dyskinesia.

Manifestations of Tardive Dyskinesia

Central manifestations of tardive dyskinesia (facial, buccal, and oral) were present in 65 (81%) of the 80 men with tardive dyskinesia and 105 (95%) of the 111 women with tardive dyskinesia. Peripheral tardive dyskinesia (body and limbs) was equally distributed between men (28 patients [35%]) and women (39 patients [35%]).

Of the central manifestations of tardive dyskinesia, hip and chewing movements were the most common (114 patients had hip movements and 111 had chewing movements), followed by tongue protrusion (82 patients), and the bon bon sign (27 patients). The least common movements were those in the periocular area (26 patients). Of the peripheral manifestations, the limbs were the most affected (41 patients had lower limb movements and 30 had upper limb movements); axial hyperkinesia was found in 18 patients.

Table 2 gives the male-female ratio, age, Simpson Rating Scale scores, and neuroleptic doses of the 20 patients with severe tardive dyskinesia. Choreoathetoid dyskinesia was present only in the women in the study group. Tardive dystonia was present in seven men and two women. Three of the patients with tardive dystonia had mild bucco-oral tardive dyskinesia, two had respiratory tardive dyskinesia, one had parkinsonian tremors in both hands, and three had tardive dystonia without any other movement disorders. Table 2 shows that tardive dystonia was noted sooner after the start of neuroleptic therapy than was choreoathetoid dyskinesia. The patients with tardive dystonia were also younger than those with choreoathetoid dyskinesia.

Eight of the nine patients with dystonia and seven of the 11 patients with dyskinesia complained about and were incapacitated by their movement disorder.

Tardive Dyskinesia, Age, and Gender

Table 3 shows that the rate of tardive dyskinesia increased with age among these patients. In women, the increase was curvilinear, but the prevalence in men decreased or stabilized around age 70.

The prevalence of tardive dyskinesia was significantly higher in men 40 years old or younger than in women of the same age group. On the other hand, moderate and severe tardive dyskinesia were more prevalent in women 71 years old or older than in men in the same age group; 33 (34%) of 98 women but only six (14%) of 44 men 71 years old or older had moderate or severe tardive dyskinesia. This difference was statistically significant ($\chi^2=6.1$, df=1, p<0.025). In the 41–70-year-old age group, tardive dyskinesia was equally distributed among the men and women (31.1% in men versus 33.1% in women). The numbers of men and women with moderate or severe tardive dyskinesia were also not statistically significantly different; 19 (12%) of the 157 men and 27 (16%) of the 172 women in this age group had moderate or severe tardive dyskinesia.

Patient Chart Analysis

Of the 191 patients who had severe (N=20), moderate (N=80), or mild (N=91) tardive dyskinesia, 155 (81%) had complete files. Nineteen of these patients had severe, 70 had moderate, and 66 had mild tardive dyskinesia. The 36 incomplete files were excluded from analysis; 20 of these patients were treated in other hospitals, and 16 had interrupted treatment in our hospital. Characteristics of the excluded patients with mild or moderate tardive dyskinesia compared with those of the patients with complete files are presented in table 4. No significant differences were found between these two groups.

Comparison of Patients With Mild, Moderate, or Severe Tardive Dyskinesia

Table 5 presents a comparison of the men and women with mild, moderate, or severe tardive dyskinesia. Men with severe tardive dyskinesia were younger than all of the other groups of patients. The male patients with mild, moderate, or severe tardive dyskinesia did not differ from each other in age at the start of neuroleptic treatment. However, among the women, those with moderate tardive dyskinesia started neuroleptic treatment at a significantly older age than did those with mild tardive dyskinesia (see table 5).

As noted in table 5, patients with mild tardive dyskinesia had a significantly greater total neuroleptic intake than did patients with moderate or severe tardive

TABLE 3. Distribution of Tardive Dyskinesia Among 558 Psychiatric Patients by Age Bracket

	Age (years)				
Diagnosis and Sex	40 or Younger[a]	41–50	51–60	61–70	71 or Older
Number of patients with tardive dyskinesia					
Mild					
Men	0	5	10	15	11
Women	0	1	13	16	20
Moderate					
Men	8	3	7	8	6
Women	1	3	3	16	25
Severe					
Men	6	0	0	1	0
Women	0	1	0	4	8
Total					
Men	14	8	17	24	17
Women	1	5	16	36	53
Patients with tardive dyskinesia as a percent of all patients in age group					
Men	22.6	17.8	28.3	46.0	38.0
Women	4.0	18.5	25.8	42.3	54.1
Number of patients without tardive dyskinesia					
Men	48	37	43	28	27
Women	24	22	46	47	45
Total number of patients					
Men	62	45	60	52	44
Women	25	27	62	83	98

[a]Men in this age group represented a significantly larger percent of the total than did women in this age group ($\chi^2=4.3$, df=1, p<0.05).

TABLE 4. Characteristics of Patients With Mild or Moderate Tardive Dyskinesia Included (N=136) and Excluded (N=35) From Study

	Age at Time of Study (years)		Age at First Exposure to Neuroleptics (years)		Male-Female Ratio	Diagnosis (number of patients)		
Group	Mean	SD	Mean	SD		Schizophrenia	Affective Disorder	Organic Disorder
Patients with moderate tardive dyskinesia								
Included (N=70)	66.9	12.7	45.9	14.2	30:40	27	22	21
Excluded (N=10)	63.8	18.8	41.3	13.8	2:8	6	4	0
Patients with mild tardive dyskinesia								
Included (N=66)	66.0	9.7	41.3	12.6	29:37	44	12	10
Excluded (N=25)	62.2	10.6	35.0	15.9	12:13	13	11	1

dyskinesia. Patients with mild tardive dyskinesia also had a higher aliphatic and piperazine phenothiazine intake, but there was no significant difference among the groups in intake of piperidine phenothiazines and haloperidol.

The most commonly prescribed drugs were the aliphatic phenothiazines; 62 (94%) of the patients with mild, 64 (91%) of the patients with moderate, and 15 (79%) of the patients with severe tardive dyskinesia were given these drugs. The next most commonly prescribed drugs were the piperazines; 54 (82%) of the patients with mild, 58 (83%) of the patients with moderate, and 11 (58%) of the patients with severe tardive dyskinesia were given these drugs. Haloperidol was next; 32 (49%) of the patients with mild, 34 (49%) of the patients with moderate, and nine (47%) of the patients with severe tardive dyskinesia received this drug. Finally, the piperidines were given to 21 (32%)

of the patients with mild, 28 (40%) of the patients with moderate, and five (26%) of the patients with severe tardive dyskinesia.

Nineteen of the 155 patients were found to have received single neuroleptics during the entire course of their treatment. Six of the 19 patients with severe tardive dyskinesia had received single neuroleptics (one man each received an aliphatic, piperazine, or haloperidol neuroleptic; one woman received an aliphatic and two women received haloperidol). Six of the 70 patients with moderate tardive dyskinesia were prescribed single neuroleptics (one man received haloperidol, three women received aliphatic phenothiazines, and two women received piperazines). Seven of the 66 patients with mild tardive dyskinesia received single neuroleptics (one man received a piperazine phenothiazine and one received haloperidol; four women received aliphatic phenothiazines and one received hal-

TABLE 5. Characteristics of 155 Male and Female Patients With Mild, Moderate, or Severe Tardive Dyskinesia

Group	Age at Time of Study (years)		Age at First Exposure to Neuroleptics (months)[a]		Duration of Hospitalization (months)		Drug-Free Periods (months)[b]		Current Neuroleptic Dose (mg/day)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients with mild tardive dyskinesia										
Men (N=29)	64.3	10.0	39.6	11.9	238.0	197.7	11.1	22.7	698.8	758.3
Women (N=37)	67.4	9.3	42.7	13.1	175.9	175.3	7.9	19.2	320.3	409.9
Total (N=66)	66.0	9.7	41.3	12.6	203.2	183.9	9.3	20.7	486.6	613.7
Patients with moderate tardive dyskinesia										
Men (N=28)	61.4	12.1	39.6	9.4	164.5	212.0	22.6	41.8	615.0	840.6
Women (N=42)	70.6	11.8	50.2	15.3	161.5	179.1	19.8	30.0	232.5	439.2
Total (N=70)	66.9	12.7	45.9	14.2	162.7	191.4	20.9	35.0	385.5	653.3
Patients with severe tardive dyskinesia										
Men (N=6)	43.8	20.1	34.2	22.7	19.5	12.8	0.5	1.2	433.3	213.7
Women (N=13)	71.0	10.4	48.2	13.2	223.2	214.9	16.8	27.9	223.5	244.3
Total (N=19)	62.4	18.8	43.8	17.4	158.8	200.7	11.7	24.1	289.7	250.0

[a]Significantly lower for women with mild tardive dyskinesia than for women with moderate tardive dyskinesia (t=2.3, df=77, p<0.05).
[b]Significantly lower for all patients with mild tardive dyskinesia than for all patients with moderate tardive dyskinesia (t=2.37, df=134, p<0.02).
[c]Significantly higher for all patients with mild tardive dyskinesia than for all patients with moderate (t=3.2, df=134, p<0.01) or severe (t=2.28, df=83, p<0.05) tardive dyskinesia.
[d]Significantly higher for all patients with mild tardive dyskinesia than for all patients with moderate tardive dyskinesia (t=4.22, df=134, p<0.001).
[e]Significantly higher for all patients with mild tardive dyskinesia than for all patients with severe tardive dyskinesia (t=2.59, df=83, p<0.02).

operidol). Thus, nine patients received only aliphatic phenothiazines, six received only haloperidol, and four received only piperazine phenothiazines.

Drug-free periods were described in the charts of 26% (N=17) of the patients with mild tardive dyskinesia but in 64% (N=45) of the patients with moderate tardive dyskinesia (χ^2=2.03, df=1, p<0.001). On the other hand, 47% (N=9) of the patients with severe tardive dyskinesia had drug-free periods. The difference between patients with mild and severe tardive dyskinesia was not significant (χ^2=3.2, df=1). Interestingly, none of the patients with tardive dystonia had drug-free periods.

As noted in table 5, the patients with mild tardive dyskinesia had significantly fewer drug-free months than did patients with moderate tardive dyskinesia but not significantly fewer than did patients with severe tardive dyskinesia.

The patients with mild, moderate, or severe tardive dyskinesia did not differ significantly from each other in the number of hospital admissions and the duration of hospitalizations (see table 5) or in the mean total amount of antidepressant and antiparkinsonian drugs prescribed (data not shown).

Description of Tardive Dyskinesia in the Patient's Files

Severe tardive dyskinesia was described in the patients' files after a mean±SD of 10.9±8.5 years of neuroleptic treatment; for men the mean was 4.6±2.9, and for women it was 13.5±8.7. Moderate tardive dyskinesia was described after a mean of 13.2±7.3 years; for men it was 11.9±6.9, and for women it was 13.9±7.5. Mild tardive dyskinesia was described after a mean of 17.0±7.8 years; for men the mean was 20.8±7.2, and for women it was 14.9±7.8.

Organic Factors and Treatments

Due to the small number of patients with severe tardive dyskinesia, we combined the patients with moderate and severe tardive dyskinesia into one moderate-to-severe tardive dyskinesia group and compared it with the group of patients with mild tardive dyskinesia. There was no difference in organic factors between the patients in the moderate-to-severe tardive dyskinesia group and those in the mild tardive dyskinesia group (see table 6). There was a mean of 1.5±1.2 organic diagnoses in the patients with moderate-to-severe tardive dyskinesia and a mean of 1.4±1.2 in the patients with mild tardive dyskinesia. Mental retardation was present significantly more often in the moderate-to-severe group than in the mild group (see table 6). ECT was given to a higher percentage of the patients with mild tardive dyskinesia than with moderate-to-severe tardive dyskinesia (see table 6). The 25 patients with mild tardive dyskinesia who received ECT were given a mean of 32.7±25.4 treatments; the 24 patients with moderate-to-severe tardive dyskinesia who received ECT were given a mean of 20.4±17.1 treatments. Similarly, the eight patients with moderate-to-severe tardive dyskinesia who had insulin comas received a mean of 28.1±20.1 treatments; the 12 pa-

TABLE 5. (continued)

| Total Neuroleptic Intake (g) (chlorpromazine equivalents) | | | | | | | | | |
| Total[c] | | Aliphatic[d] | | Piperidine | | Piperazine[e] | | Haloperidol | |
Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
5101.4	3516.3	1905.7	1540.4	111.1	234.6	2119.4	2205.5	665.4	1927.8
3209.8	2384.5	1359.3	1410.6	133.0	273.0	1387.0	1567.0	331.8	792.8
4041.0	3266.8	1599.0	1483.0	123.4	255.0	1840.7	1929.3	478.4	1406.0
3273.4	2819.3	883.6	931.0	206.1	487.4	1313.7	1220.0	776.8	2058.6
1996.7	1741.0	642.3	774.8	43.4	120.5	1098.0	1335.2	208.8	648.3
2507.4	2304.0	738.8	842.6	108.5	328.7	1184.2	1285.7	436.0	1409.5
1100.3	980.2	206.5	245.8	6.0	12.0	333.0	516.2	554.8	686.5
2729.8	2476.7	1280.0	1555.5	117.4	258.5	817.6	1268.5	496.9	852.8
2215.3	2227.5	940.0	1375.8	82.2	217.8	664.6	1095.6	515.0	785.1

tients with mild tardive dyskinesia who had insulin comas received a mean of 49.0±31.1 treatments.

DISCUSSION

Tardive dyskinesia was present in 34% of our patient group. This is a higher rate than the estimated 20% prevalence of tardive dyskinesia in similar groups (16). However, our sample included a large number of older patients, which might account for the higher prevalence of tardive dyskinesia (16).

We found no statistically significant difference in the prevalence of tardive dyskinesia between men and women (30% versus 38%, respectively), although the women were significantly older than the men. The literature is divided on this issue. Some studies indicated that women have a higher prevalence of tardive dyskinesia than men (17), others found no difference (18), and still others found that men had a higher prevalence of tardive dyskinesia than women (19).

In our study, the prevalence of tardive dyskinesia increased with age. However, the distribution of the severity of tardive dyskinesia differed according to gender. More men than women who were 40 years old or younger had tardive dyskinesia (23% versus 4%). More men than women in this age group also had moderate and severe tardive dyskinesia. On the other hand, more women than men who were 71 years old or older had moderate and severe tardive dyskinesia (34% versus 14%). Moderate-to-severe tardive dyskinesia was equally distributed in both sexes in the 41–

70-year-old age group (16% of the women and 12% of the men). These findings confirm those of other studies (8, 20).

The prevalence of severe tardive dyskinesia in our patient group was 3.6% (20 of 558). We found 11 studies (including ours) that discuss severe tardive dyskinesia (6, 17, 19–26); these studies included 11,484 patients. The mean prevalence of severe tardive dyskinesia in these studies was 4.3% (range=0%–12.5%). In men, the weighted mean prevalence of severe tardive dyskinesia was 3.4% (range=0%–9.6%), and in women it was 5.1% (range=0%–15.2%). In five studies (6, 17, 21, 23, 26), women had a higher prevalence of severe tardive dyskinesia than men, and in six (19, 20, 22, 24, 25, and our own), no gender difference was found.

The manifestations of severe tardive dyskinesia differed in men and women. Although tardive dystonia was the most common manifestation of severe tardive dyskinesia in young men, choreoathetoid dyskinesia was more common in elderly women. It is to be noted that patients with tardive dystonia also had other manifestations of tardive dyskinesia and patients with choreoathetoid dyskinesia had some symptoms of tardive dystonia. These findings are in agreement with those of Gardos et al. (7), who found that four of seven patients with severe tardive dyskinesia were women (mean age=67.5 years), compared with six of eight men who had severe tardive dystonia (mean age=34.3 years). Patients suffering from tardive dystonia complain of their movement disorder, but not all patients with severe tardive dyskinesia do so. Therefore, using

TABLE 6. Organic Factors and Treatments in 155 Patients With Moderate-to-Severe or Mild Tardive Dyskinesia

Factor or Treatment	Patients With Moderate-to-Severe Tardive Dyskinesia (N=89)		Patients With Mild Tardive Dyskinesia (N=66)	
	N	%	N	%
Diabetes mellitus	14	15.7	9	13.6
ECT	24	27.0	25	37.9
Insulin comas	8	9.0	12	18.2
Cardiovascular disease	19	21.3	14	21.2
Lobotomy	3	3.4	3	4.5
Alcohol abuse	11	12.4	5	7.6
Cancer	4	4.5	5	7.6
Thyroid disorders	5	5.6	6	9.1
Chronic lung disease	6	6.7	5	7.6
Mental retardation[a]	15	16.9	2	3.0
Epilepsy	4	4.5	5	7.6
Dementia	8	9.0	4	6.1

[a]Significantly more patients with moderate-to-severe tardive dyskinesia had this factor ($\chi^2=7.4$, df=1, p<0.001).

subjective and objective criteria of incapacitation for a diagnosis of severe tardive dyskinesia may not be the best way of diagnosing this disorder. On the other hand, as shown in table 2, using the total score for severity may be misleading.

Efforts to relate tardive dyskinesia to a particular type of neuroleptic have been futile (27). In this study, we found 19 patients who received one neuroleptic during the entire course of their treatment. All phenothiazine groups (except piperidines) were represented.

Interestingly, age at onset of neuroleptic treatment has been considered a factor in the development of tardive dyskinesia (28). Patients who received neuroleptics for the first time later in life were found to develop tardive dyskinesia that was more severe and that developed in a shorter period than patients who received neuroleptics earlier in life (28). In this study, we found that women with moderate tardive dyskinesia received neuroleptics at a significantly later age than did women with mild tardive dyskinesia.

In our study group, patients with mild tardive dyskinesia received a greater total amount of neuroleptics than did patients with moderate or severe tardive dyskinesia, although the duration of treatment was not significantly different. This may be an epiphenomenon, however. It is possible that the treating physician noticed the tardive dyskinesia and lowered the dose in those patients with severe tardive dyskinesia. This may partly explain the higher current neuroleptic dose in patients with mild tardive dyskinesia than in those with more severe forms (see table 1) and the consequent masking effect of neuroleptics on tardive dyskinesia symptoms. It is also possible that the lower total neuroleptic dose and total aliphatic phenothiazine dose noted in men with severe tardive dyskinesia may be due to the very young age of this subgroup, which had a substantially lower total duration of neuroleptic exposure and were probably treated in an era when

aliphatic drugs were less likely to be prescribed. On the other hand, it is possible that patients who develop severe tardive dyskinesia do so faster and with relatively smaller amounts of neuroleptics than do patients with mild tardive dyskinesia (28). Susceptibility factors have been suggested (29, 30). In our study, piperazine phenothiazines as well as aliphatic phenothiazines were more often used in the treatment of mild tardive dyskinesia than in the moderate and severe forms. This finding was unexpected, especially in view of some previous reports (20, 31) that piperazine compounds are more often prescribed for patients with tardive dyskinesia.

Our study confirms the idea that drug-free periods may be an important factor in the development of more severe forms of tardive dyskinesia. Several animal (32) and human (33) studies have demonstrated that drug-free periods are more common in the history of patients with tardive dyskinesia, but others have not confirmed this finding (2).

Factors not found to differentiate mild, moderate, and severe forms of tardive dyskinesia include duration and number of hospitalizations as well as organic factors and treatments.

In conclusion, severe tardive dyskinesia was found in 3.6% of our patient group. Young men were found to have more severe tardive dyskinesia with a shorter duration of neuroleptic treatment than women of the same age. On the other hand, women 71 years old and older were found to have more severe tardive dyskinesia than men of the same age. Drug-free periods were found more commonly and for longer periods of time in moderate and severe tardive dyskinesia than in mild forms.

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Cocaine Abuse Among Schizophrenic Patients

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Initial studies have indicated that stimulant abuse is prevalent among schizophrenic persons. To assess the phenomenon of cocaine abuse by patients with schizophrenia, 17 male cocaine-abusing schizophrenic patients were compared with 22 male schizophrenic patients who did not use cocaine. The cocaine-abusing subjects had been hospitalized more frequently, were more likely to be of the paranoid subtype, and were more likely to be depressed at the time of interview. It appears that cocaine abuse may influence both the psychopathologic presentation of schizophrenic patients and the intensity of care that they require.
(Am J Psychiatry 1990; 147:1164–1167)

C ocaine abuse has grown to epidemic proportions in the United States (1). The rewarding effects of cocaine are thought to be secondary to a functional increase of dopamine at the synapse (2). An interesting subgroup of cocaine-abusing individuals are those who suffer from schizophrenia. The dopamine hypothesis of schizophrenia posits that the psychotic symptoms of schizophrenic patients are produced by a functional excess of dopamine in certain brain areas (3). Considering the dopamine-stimulating and potentially psychotomimetic properties of cocaine, it is counter to common sense that patients suffering from psychotic disorders would self-administer this drug. In spite of this, several studies have indicated that stimulant abuse is more prevalent in schizophrenic individuals than in control populations (4, 5).

Theories attempting to address the complex interaction between the abuse of psychoactive substances and psychopathology have commented on both psychoactive drug use as a cause of psychiatric symptoms and use of drugs of abuse as self-medication for psychiatric symptoms (5). Stimulants have been reported to activate endogenous psychoses (6, 7) and might be ex-

pected to contribute to relapse or worsen the course of a preexisting psychosis. Richard et al. (8) reported a higher rate of recent stimulant use by hospitalized schizophrenic patients than by hospitalized patients with other psychiatric diagnoses. On the other hand, several investigators have reported improvements in negative symptoms of schizophrenia after treatment with dopamine agonists (9–11). Thus, the interaction between the use of cocaine and schizophrenia may include elements of drug-induced exacerbation as well as amelioration of specific symptoms.

Another issue in this patient group is the potential relation between stimulant use and tardive dyskinesia. Although controversial, a widely held theory is that tardive dyskinesia is caused by a supersensitivity of dopamine receptors (12). It has also been postulated that chronic cocaine use may lead to a supersensitivity of dopamine receptors (2). One might speculate that stimulant use could precipitate or worsen neuroleptic-induced tardive dyskinesia.

This preliminary study was designed to investigate the phenomenon of cocaine abuse in schizophrenic patients. Cocaine-abusing schizophrenic patients were compared to schizophrenic patients who were nonusers with respect to positive and negative symptoms of schizophrenia, course and subtype of illness, and evidence of tardive dyskinesia. We also explored the subjective experiences and reports of motivating factors for stimulant use.

METHOD

Subjects were recruited from an outpatient clinic at the Charleston Veterans Administration Medical Center. Stabilized members of outpatient groups with chart diagnoses of either schizophrenia or schizoaffective disorder were selected for interview. Of this group, 17 male patients who met the *DSM-III-R* criteria for schizophrenia and admitted to using cocaine at least twice in the last 6 months were compared with 22 male patients matched for age and duration of illness who met the *DSM-III-R* criteria for schizophrenia but denied using cocaine and had had documented negative urine drug screens in the year before interview. In all

TABLE 1. Diagnostic Subtypes, Current Depression, and Previous Suicide Attempts Among Male Schizophrenic Patients Who Were or Were Not Cocaine Abusers

Variable	Nonabusers of Cocaine (N=22)		Cocaine Abusers (N=17)		χ^2 (df=1)	p
	N	%	N	%		
Schizophrenic subtype						
Paranoid	1	4.5	8	47.1	7.30	<0.01
Undifferentiated	17	77.3	3	17.6	11.36	<0.01
Schizoaffective	4	18.2	6	35.3	0.71	n.s.
Current major depression	4	18.2	10	58.8	5.23	<0.05
Previous suicide attempts	6	27.3	8	47.1	0.92	n.s.

TABLE 2. Demographic Characteristics of Male Schizophrenic Patients Who Were or Were Not Cocaine Abusers

Variable	Nonabusers of Cocaine (N=22)		Cocaine Abusers (N=17)		Comparison
	Mean	SD	Mean	SD	
Age (years)	37.5	5.8	34.4	1.2	t=1.3, df=37, n.s.
Duration of illness (years)	14.7	5.8	13.0	5.1	t=1.0, df=37, n.s.
Number of hospitalizations during lifetime	9.5	6.5	13.4	6.9	t=1.8, df=37, p<0.10
Number of hospitalizations during past year	1.0	8.0	1.9	1.0	χ^2=8.33, df=2, p<0.05

cases the diagnosis of schizophrenia preceded the stimulant abuse by a mean±SD of 5.2±1.1 years (range= 1.0–16.0 years).

After obtaining informed consent, we administered to each subject the portions of the Structured Clinical Interview for DSM-III-R (SCID) (13) devoted to psychotic disorders, affective disorders, and substance abuse. Only patients whose diagnoses of schizophrenia were confirmed by the SCID were included in the study. We used the Brief Psychiatric Rating Scale (BPRS) (14) to rate positive and negative schizophrenic symptoms. Absence of a symptom was rated as zero. BPRS ratings for motor retardation, blunted affect, and emotional withdrawal were grouped as the negative symptom cluster, and the ratings for hallucinatory behavior, unusual thought content, and conceptual disorganization were grouped as the positive symptom cluster (15). We also rated the subjects on the Abnormal Involuntary Movements Scale (AIMS) (16). Diagnostic interviews and rating scales were done by a psychiatrist (K.B.) who was not blind to patients' history of drug use. All cocaine-abusing subjects denied cocaine use in the week before interview.

Additional information concerning length of illness, number of prior hospitalizations, employment status, and dose of maintenance neuroleptic was obtained from an unstructured interview and chart review. In addition, we asked each cocaine-abusing subject to describe the subjective effects of cocaine use with particular attention to the effect on hallucinations, paranoia, and mood.

Student's t test was used to compare the groups with respect to age, duration of illness, number of prior hospitalizations, neuroleptic dosage, and scores on the BPRS and AIMS. Chi-square (2×2) analysis with Yates' correction factor was used for comparison of subtype of schizophrenia, current depression, suicide attempts, and employment status. Number of hospitalizations in the year before interview was analyzed by chi-square (3×2).

RESULTS

Table 1 illustrates the distribution of diagnostic subcategories determined by the SCID for the two groups. The cocaine-abusing schizophrenic subjects were more likely to have diagnoses of the paranoid subtype, whereas those who were not cocaine abusers were more frequently diagnosed as having the undifferentiated subtype. Significantly more cocaine-abusing subjects also met the criteria for a current major depressive episode at the time of interview.

Table 2 displays the demographic and psychosocial variables in the cocaine-abusing and nonabusing groups. The cocaine-abusing patients had had significantly more hospitalizations in the past year, and there was a trend toward a greater number of hospitalizations during their lifetimes in that group. There were no significant differences between the two groups in age, duration of illness, or employment history.

There was a trend (t=1.6, df=37, p<0.10) toward higher AIMS scores in the cocaine-abusing group: the abusers had a mean±SD score of 4.3±3.1, and the nonabusers 2.8±2.2. There were no significant differences in mean±SD current neuroleptic dose in chlorpromazine equivalents (abusers, 2165±1531; nonabusers, 1764±1491), total BPRS score (abusers, 23.4±9.5; nonabusers, 19.9±6.6), positive symptom cluster score (abusers, 6.6±3.0; nonabusers, 7.2±7.0), and negative symptom cluster score (abusers, 6.3±4.6; nonabusers, 7.5±4.8).

In the year before interview, each subject had had at least one urine drug screen. Urine drug screens were done a mean±SD of 1.6±0.9 times (range=1–3) in the group that did not use cocaine, and all of their urine drug screens were negative. In the cocaine-abusing group, urine drug screens were done 2.9±1.3 times (range=1–6), and 11 of the 17 subjects had had

at least one urine drug screen that was positive for cocaine.

Nine of the 17 cocaine-abusing subjects had histories of polysubstance abuse, including marijuana, LSD, and narcotics. The only drug besides cocaine used by this group in the 2 years before interview was marijuana; five admitted to marijuana use approximately once a month, and two reported marijuana use more than once a week. Nine of this group reported alcohol use approximately once a week, and two met the criteria for current alcohol abuse. In the comparison group, six patients reported occasional marijuana use, 10 stated that they used alcohol approximately once a week, and two met the criteria for alcohol abuse. Subjects in the comparison group denied any other drug use. There were no significant differences in marijuana or alcohol use between the two groups.

Patterns of cocaine use varied considerably among the cocaine-abusing subjects. In the 6 months before interview, six of the subjects reported daily use for at least 2 months, four claimed use about 2–3 times a week, four claimed use approximately once a week, one reported binges for 2–3 days approximately once a month, and two reported two 3-to-4-day binges during the time in question. There was no correlation between amount of use and patients' presentation.

Fifteen of the 17 cocaine-abusing subjects stated that cocaine-induced improvement in mood was their main motivation for use. Of the remaining patients, one stated that the "rush" was the main reason for using cocaine, and the other stated that he did not know why he used cocaine. Other comments included "I feel more talkative and friendly" and "I feel better about myself." Three subjects said cocaine worsened hallucinations, seven said cocaine decreased the severity of their hallucinations, and seven said cocaine had no effect on hallucinations. Only two patients reported an exacerbation of paranoia under the influence of cocaine.

DISCUSSION

Our data suggest several interactions between the use of cocaine and the course and severity of schizophrenic illness. The finding of a significantly higher number of hospitalizations in the past year in the cocaine-abusing group and a trend toward a higher number of hospitalizations during their lifetimes in this group suggests that cocaine use may worsen the course of schizophrenia and contribute to relapse. This agrees with the finding by Richard et al. (8) of increased stimulant use in relapsing schizophrenic patients.

More paranoid schizophrenic subjects were found in the cocaine-abusing group, while chronic undifferentiated schizophrenia was the most common diagnosis in the group of nonusers. It is possible that cocaine, which can produce paranoid symptoms in nonpsychotic individuals (17), increased the expression of paranoid symptoms in the cocaine-using group. How-

ever, only two subjects stated that cocaine acutely worsened their paranoia. It is possible that lack of insight or inability to make logical connections between cocaine use and its effects could explain the lack of increase in paranoia reported by our patients.

The observation that significantly more cocaine-abusing schizophrenic patients were currently depressed suggests that either these patients were using cocaine to self-medicate an underlying depression or that cocaine use precipitated depression in these individuals. Other investigators have also reported a high incidence of affective disorder (18) in a stimulant-abusing patient population.

The trend toward higher AIMS scores in the cocaine-abusing group is a finding with disturbing implications. Dixon et al. (19) found higher AIMS scores for a group of schizophrenic subjects who abused a wide variety of substances than for control subjects. Several studies have shown increased dopamine receptor binding after chronic cocaine administration (20). It is possible that chronic cocaine use can produce a supersensitivity of dopamine receptors, which could then potentiate the neuroleptic-induced supersensitivity that some investigators think is responsible for tardive dyskinesia. In this light, it is of interest that there was no significant difference in current mean neuroleptic dose between the two groups in our study.

The subjective drug experience of our stimulant-abusing schizophrenic subjects is also interesting. The subjects consistently reported mood elevation as the motivation for cocaine use. In addition, some noted that cocaine made them feel more sociable and talkative. This could be viewed as self-medication of 1) negative symptoms of schizophrenia, 2) depression, or 3) neuroleptic side effects. The absence of a difference between the two groups in BPRS negative and positive symptom cluster scores argues against the notion that the cocaine-abusing patients were self-medicating their negative symptoms of schizophrenia. One might expect a dopamine agonist to exacerbate hallucinations and paranoia, but this was seldom reported by our patients. Some investigators have failed to find worsening of hallucinations after the administration of amphetamines to schizophrenic subjects (6). Neuroleptics may also differentially block the dopamine tracts which mediate psychosis, so that during neuroleptic treatment schizophrenic patients experience the euphoric effects of cocaine without an exacerbation of positive symptoms.

In summary, although this was a preliminary study, there were several provocative findings. The cocaine-abusing schizophrenic patients had been hospitalized more frequently, were more likely to have a diagnosis of the paranoid subtype, and were more likely to be depressed at the time of interview than a matched group that did not use cocaine. Additionally, in the cocaine-abusing group there was a trend toward higher AIMS scores. It appears that the interaction between use of cocaine and schizophrenia may include elements of causality as well as self-medication. The

nonblind nature of the ratings limits interpretation of the data; rater bias regarding potential effects of stimulant use on subtype of schizophrenia, depression, or movement disorders may have influenced the ratings. As this study was limited by its small sample size, lack of corroboration of reported drug use, and the nonblind ratings, larger and better controlled studies will be necessary to further clarify the issues raised.

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Maladaptive Denial of Physical Illness:
A Proposal for *DSM-IV*

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Denial of physical illness is a commonly encountered problem in consultation-liaison psychiatry. Although there is an extensive literature on denial, it has virtually ignored the diagnostic issues raised by the individual whose denial of physical illness is clearly maladaptive. The authors propose that DSM-IV include a subtype of adjustment disorder called "with maladaptive denial of physical disorder." They discuss this new category, its differential diagnosis, and the benefits to clinical practice of this proposed addition to diagnostic classification.
(Am J Psychiatry 1990; 147:1168–1172)

D enial of physical illness is a commonly encountered problem in consultation-liaison psychiatry. The term "denial" has become part of the language of the hospital ward. In a broader sense, denial has become integral to our thinking about the psychological response to physical illness. The literature on denial has focused on its classification (1), psychological function (2), quantification (3), misuse (4), and lack of a standard definition (5) but has virtually ignored the diagnostic issues raised by the individual whose denial of physical illness is clearly maladaptive.

During a study of the utilization of the *DSM-III-R* classification system in a consultation-liaison psychiatry setting, we encountered many patients for whom maladaptive denial of physical illness was the focus of clinical attention. The only reference to maladaptive denial of physical illness in *DSM-III-R* is a nondiagnostic category that is outside the classification of mental disorders, a V code for noncompliance with treatment. The text for that category indicates its lack of specificity: "This category can be used when the focus of attention or treatment is noncompliance with medical treatment that is apparently not due to a mental disorder. Examples include: irrationally motivated noncompliance due to denial of illness, noncompliance due to religious beliefs, and decisions based on per-

sonal value judgments about the advantages and disadvantages of the proposed treatment."

DSM-III-R does have a diagnosis, psychological factors affecting physical condition, the name of which suggests that it might be appropriate for diagnosing maladaptive denial of physical illness. However, the text and criteria for the category indicate that it is intended for noting the direct physiological impact of psychological factors, as in the exacerbation of ulcerative colitis by stress. In denial, psychological factors may lead to behavior, such as noncompliance with a treatment plan, that may exacerbate a physical disorder. However, the psychological factor in these cases only indirectly affects the physical disorder.

To address the problem of diagnosis for individuals whose predominant problem is noncompliance due to maladaptive denial of physical illness, we propose that *DSM-IV* add to the list of eight subtypes of adjustment disorder a new subtype called "with maladaptive denial of physical illness." In this article we review the concept of denial of physical illness, present the text for the proposed subtype, and discuss its differential diagnosis and clinical utility.

REVIEW OF THE CONCEPT OF DENIAL OF PHYSICAL ILLNESS

Standard texts in consultation-liaison psychiatry (6–8) devote considerable space to the description and management of denial of physical illness. However, there is little clarity about what is meant by denial, what its essential features are, how it should be assessed, and under what conditions the terms "healthy/adaptive" or "pathological/maladaptive" should be applied.

Anna Freud (9) described denial as a defense mechanism that has the goal of reducing unpleasant affects by means of disavowing aspects of reality. Vaillant (1) and other psychoanalytic writers (10) focused on the psychotic-like disavowal of reality and classified denial as a primitive defense. Weisman (11) divided denial according to what was being denied (the fact of the illness, the implications, or death). Breznitz (12), in his classification of seven types of denial, stressed the threat to the individual. Janis (13), noting that situational factors, such as inadequate information being

given to the individual, contribute to the use of denial, suggested that the term "pathological denial" be restricted to situations of acute danger. The many attempts to operationalize the assessment of denial or to index its severity by means of rating scales have differed in the relative emphasis given to disavowal of reality and to the absence of anxiety (14). This confusion in the definition of denial likely accounts for the widely varying reports of its frequency in samples of medically ill patients (14–16).

Furthermore, there is no consensus about whether the expressions "healthy" and "pathological" denote the extent to which reality is disavowed, the degree to which an expected affect is absent, or outcome. Outcome studies in cardiac (17) and cancer (18) patients have indicated that denial can serve important adaptive functions. However, many have suggested that what is prognostically important in healthy denial may have less to do with the disavowal of a stressful reality (i.e., the denial) than with other aspects of the denier's approach to life (19), such as psychological hardiness (20) or resilience (21). These researchers thereby question the application of the terms "healthy" and "pathological" to denial even when outcome is the basis of the distinction.

Some authors have argued that confusion about what is meant by the term "denial" contributes to poor clinical practice. Cousins (5) noted that the term is often misused in situations in which patients merely seek alternative opinions, are noncompliant in order to avail themselves of nonstandard approaches to health care, or fail to conform to physicians' expectation of a normal emotional response to physical illness. Shelp and Perl (4) cited examples in which denial is misapplied to patients whose perceptual or cognitive impairment, neurological neglect syndromes, or different "risk assessments" explain their refusal to accept their physicians' diagnosis, prognosis, or recommended treatment. Such misuse of the term can lead to morally questionable paternalistic interventions, such as the justification of involuntary treatment.

DEVELOPMENT OF THE PROPOSED NEW SUBTYPE

In our experience on a psychiatric consultation service, approximately 10% of the consultations involved the evaluation of patients who refused treatment. This led to our spending much time discussing denial as one of several explanations for treatment refusal or noncompliance. These discussions made clear the need for a precise definition of the term. For example, the patient who refuses treatment at least in part because he or she has received inadequate information or has made an assessment of the risks of treatment which differs from that of the physician clearly requires a different approach than the patient for whom a thorough evaluation reveals no apparent explanation except disavowal of the presence or significance of the illness—denial more narrowly defined.

As an operational definition of maladaptive denial evolved, we recognized that in some cases (e.g., grossly psychotic patients), the denial was merely a symptom of a diagnosable psychotic disorder, such as schizophrenia or major depression with psychotic features. However, for many other patients, the denial was the main symptom of a maladaptive pattern of response for which there was no suitable DSM-III-R diagnosis. In such cases, we concluded that clinical practice would be improved by a new diagnosis whose core feature is maladaptive denial of physical illness. The availability of such a diagnosis, with inclusion and exclusion criteria, would facilitate differential diagnosis in this often difficult area.

Since the concept of denial has always involved the notion of adaptation to stress, maladaptive denial of physical illness lends itself to conceptualization as a subtype of adjustment disorder. We propose the following text for this subtype, adjustment disorder with maladaptive denial of physical disorder.

This category should be used when, as a reaction to the symptoms, signs, or diagnosis of a physical illness, the predominant response is persistent denial of having a physical disorder that exposes the individual to a significantly higher risk of serious physical illness or death.

The denial takes the form of the individual asserting that he or she does not have the physical disorder or of behaving in a way that indicates that he or she minimizes the significance of the disorder. This occurs in the face of obvious physical manifestations of the disorder or in spite of the patient's having been adequately informed of its presence by a doctor.

Not included are instances in which the individual not only denies having the disorder but is in any other way delusional about the disorder, e.g., believing that doctors are trying to trick him or her into undergoing an experimental treatment. Also not included are situations in which the individual refuses treatment or lifestyle changes that caregivers believe are optimal after having made an informed and considered evaluation of the risks and benefits of these changes. Also not included are situations in which the individual refuses treatment because it violates his or her religious or subcultural belief system.

DIFFERENTIAL DIAGNOSIS

The following case vignettes illustrate the differential diagnosis of this disorder from other conditions.

Case 1. Ms. A, a 60-year-old woman, was admitted to the hospital with a fractured pelvis. When X-rays revealed lytic lesions suggesting metastatic disease and a suspicious breast mass was palpated, biopsy was recommended. The patient refused the biopsy and all blood work-ups, claiming that her only problem was the fracture. She was shown the X-rays, and it was carefully explained that they indicated a carcinoma and that without a further work-up she would likely get much sicker. She said, "That is your interpretation. Please just leave me alone." The consulting psychiatrist met with the patient and family members on several occasions in an effort to understand the patient's reluctance to acknowl-

edge her illness. Throughout, Ms. A maintained her view that she was not ill and that therefore no treatment interventions were necessary.

This case illustrates an extreme form of denial: disavowal of the physical illness itself in the face of adequate explanation.

Case 2. Mr. B, a 56-year-old man who had suffered his third massive myocardial infarction 2 days earlier, was found doing push-ups and other strenuous exercises in the hospital. When he requested to leave the hospital later the same day, he explained to the psychiatric consultant that he was aware that he had had a "small heart attack" but believed that the best way to manage the continuing chest pain was to "exercise through it."

This case illustrates another form of denial: acknowledgment of the illness but behavior that indicates a failure to appreciate its significance. In addition to the diagnosis of adjustment disorder with maladaptive denial of physical illness, further evaluation of this patient also suggested the diagnosis of narcissistic personality disorder. The therapist, by acknowledging the patient's need to consider himself special and invulnerable, was able to convince him of the need for modification of his lifestyle.

Case 3. Ms. C, a 71-year-old woman with lung cancer refractory to initial courses of radiation and chemotherapy, suffered a cerebrovascular accident that left her with a hemiparesis. After extensive discussions with her husband, daughter, and family physician regarding the risks and benefits of further treatment for her lung cancer, she refused her oncologist's recommendation of additional chemotherapy. She said that she had "been through enough," since the side effects of the therapy were so unpleasant and the potential benefits uncertain. She was willing to let her disease "run its course."

In this case the refusal of the recommended treatment cannot be ascribed to denial, since the patient appears to have made a considered and informed decision regarding the advisability of further treatment, even though her refusal of the treatment probably put her at higher risk for an earlier death.

Case 4. Mr. D, a 24-year-old man with AIDS, refused treatment during hospitalization, claiming he was not ill and had never been told that he had AIDS. He subsequently revealed that he believed that his physicians had fabricated his diagnosis in order to hold him hostage and experiment on him.

When the disavowal of reality extends beyond the question of the presence or absence of the illness, as in this case, a psychotic disorder, rather than an adjustment disorder, should be diagnosed. (In rare cases, adjustment disorder with denial of physical disorder could be diagnosed in addition to an *unrelated* psychotic disorder.)

Case 5. Mr. E, a 48-year-old extremely obese man with a cardiomyopathy, sneaked into the hospital pantry nightly despite warnings about the impact of his weight on his cardiac problem. He stated, "I know I should lose weight, and I want to, but I can't help myself."

When a patient is merely *unable* to comply with treatment recommendations or lifestyle changes because the advised changes require him or her to overcome a compulsive or addictive behavior, it is not considered denial.

Case 6. Mr. F, a 24-year-old man, was paralyzed from the waist down because of a bullet wound through his spine. Although told by his physicians that he would never be able to walk unassisted, he insisted that he would. He participated fully in physical therapy.

This patient, with his claim that he would be able to walk unassisted, was denying the significance of his physical illness. However, since his disavowal did not lead him to avoid rehabilitative efforts, he was not exposing himself to a higher risk of subsequent illness. Therefore, maladaptive denial would not be diagnosed.

Case 7. Ms. G, a 27-year-old pregnant woman with borderline personality disorder and a history of crack cocaine abuse, was found to have a placenta previa after near-fatal vaginal bleeding. Despite extensive attempts to persuade her to stay in bed at the hospital, she insisted that she must leave, explaining, "I know I can bleed to death, but if I start bleeding, I will come back. If I bleed too fast I will die. I don't care. I can't stand staying in this bed anymore."

This patient's noncompliance was due to her poor judgment and impulsivity, features of her borderline personality disorder. The noncompliance did not signify denial because she did not fail to appreciate the seriousness of her situation.

Case 8. Ms. H, a 39-year-old woman, had throughout her life studied various forms of alternative medical therapies, including megavitamins, herbal remedies, and massage. When she fractured her leg, she considered the advice of her family but refused to go to a physician to have X-rays or casting of the limb as they suggested. Instead, insisting that a nonstandard approach would be helpful, she consulted her library of alternative remedies.

In this case the individual refused standard medical care because of her commitment to a subculture that believes in the value of alternative approaches to health care. Although the patient was clearly subjecting herself to complications of the fracture, the diagnosis of denial would not be made.

QUESTIONS RAISED BY THIS DIAGNOSIS

The proposed diagnosis raises several questions, which we address in the following paragraphs.

Why do you focus on denial of physical illness rather

than the many other forms of denial that patients may exhibit, such as denial of loss of a relationship or denial of financial difficulties? It is true that denial is used as a defense in a variety of stressful situations. However, denial of physical illness is much more likely to directly cause behavior that comes to clinical attention, since it often involves refusal of treatment that places the individual at risk for substantial harm. Although it is certainly possible to add other subtypes of adjustment disorder for other forms of denial, we doubt that any of them would fulfill a real clinical need, as we believe this subtypes does.

Will this diagnosis discourage attention to coexisting axis II pathology or to efforts to understand the meaning of the illness to the patient? It should not. As case 2 illustrates, attention to a coexisting axis II diagnosis and the specific meaning of the illness to the patient will be necessary for optimal treatment, as is the case with the other axis I disorders.

If someone totally denies the presence of a physical illness, why is this not a psychotic symptom, deserving a diagnosis of psychosis? In a psychotic disorder, the individual not only has impaired reality testing but creates a new reality. In maladaptive denial of physical illness, the individual is insisting on the old reality (his or her healthy self) rather than creating a new reality. Therefore, a diagnosis of psychosis is not appropriate.

Doesn't the proposed new category give diagnostic status to a symptom? There are several symptoms in DSM-III-R, such as many of the sexual dysfunctions, that are given diagnostic status when they are not due to another mental disorder. In addition, the other adjustment disorder subtypes, such as adjustment disorder with anxious mood, give diagnostic status to a pattern of symptoms.

Instead of having a separate category for maladaptive denial of physical illness, why not have a classification of atypical illness behavior that includes other reasons for noncompliance, such as lack of information, religious beliefs, or a disturbed doctor-patient relationship (22)? Maladaptive denial of physical illness is one form of atypical illness behavior but, unlike other atypical illness behaviors, such as those due to religious beliefs, it is usefully conceptualized as a mental disorder. Furthermore, from a clinical perspective, maladaptive denial of physical illness has different management implications than do other atypical forms of illness behavior.

The diagnosis of adjustment disorder is limited to cases in which the disturbance lasts less than 6 months. How would cases of chronic maladaptive denial of physical illness be handled? This problem is also present with other maladaptive responses to chronic stressors (lasting longer than 6 months), such as mild depression in the setting of chronic marital discord, which, according to the DSM-III-R criteria, cannot be diagnosed as adjustment disorder. One solution would be to have two forms of adjustment disorder: acute (with a duration of less than 6 months) and chronic (with a duration of more than 6 months). (The DSM-

IV committee is actively considering dropping the DSM-III-R 6-month duration requirement.)

Does the diagnosis of adjustment disorder with maladaptive denial of physical illness justify involuntary treatment? Not by itself. The legal concept of incompetence that justifies involuntary treatment involves considerations beyond the scope of diagnosis, such as the complex balance of patient autonomy versus possible untoward outcome.

Is there sufficient empirical support for this proposed diagnosis? First of all, we are not suggesting a new diagnosis; we are merely proposing the addition of a subtype to the eight that are already listed in DSM-III-R. Although the prevalence of this proposed subtype diagnosis in liaison psychiatry settings has not yet been determined, it is clear that the problem the diagnosis addresses is common and well-recognized. The systematic study of maladaptive denial of physical illness has been difficult up to now because of the absence of a consensus definition, which would be provided by this diagnosis.

CONCLUSIONS

The addition to DSM-IV of a diagnosis of adjustment disorder with maladaptive denial of physical illness would improve clinical care by providing criteria for the concept of maladaptive denial. Its inclusion in DSM-IV would encourage a more thoughtful evaluation of the reasons for noncompliance or treatment refusal, and the diagnosis would also facilitate research in this important area of clinical psychiatry.

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Variability in the Application of Contemporary Diagnostic Criteria: Endogenous Depression as an Example

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Specified diagnostic criteria have been credited, in part, with improving diagnostic reliability. The authors hypothesize that nonuniform application of these criteria across different research centers has been one factor responsible for the failure to replicate research findings. For example, researchers using a narrow interpretation of the Research Diagnostic Criteria (RDC) have found a highly significant association between endogenous depression and a positive dexamethasone suppression test result, whereas researchers using a broad interpretation have failed to find the predicted relationship. The authors used two interpretations of the RDC and DSM-III endogenous/melancholia criteria to diagnose 60 depressed patients and found significant differences in rates of diagnoses and symptoms.
(Am J Psychiatry 1990; 147:1173–1179)

The 1980s were characterized by the rapid development of sophisticated technology, which accelerated the search for specific anatomic, physiologic, metabolic, genetic, and hormonal correlates of psychiatric disorders. At the same time, studies and discussions of diagnostic reliability, so prevalent in the 1960s and 1970s, all but disappeared. The landmark U.S.-U.K. study of the diagnosis of schizophrenia demonstrated systematic differences between American and European psychiatrists in their definitions of schizophrenia and highlighted the need for operational diagnostic criteria (1). However, the present widespread use of specified criteria means only that clinicians and researchers may be using the same criteria; it does not mean that the criteria are being used similarly.

During the past 4 years we have published several papers on the validity of the endogenous subtype of major depression (2–8). During this time we also conferred with other researchers in this area to understand the discrepancies between studies. These informal discussions raised the question of whether criteria-based definitions of endogenous depression have been applied consistently across research centers.

The *DSM-III* criteria for major depression with melancholia and the Research Diagnostic Criteria (RDC) (9) for major depressive disorder, endogenous subtype, have been the two most widely studied criteria-based definitions of endogenous depression, and the most frequently studied correlate of endogenous depression has been the dexamethasone suppression test (DST). The DST was the focus of a large amount of research during the past decade, and the accumulated data suggest that it is neither a sensitive nor specific diagnostic test (10–14). Nevertheless, a review of studies examining DST results in RDC endogenous depression illustrates how variations in diagnostic practices may affect the conclusions regarding the association between biological tests and diagnosis.

Several years ago we summarized the results of 11 studies examining the relationship between the DST and RDC endogenous depression (2). We are now aware of 19 studies examining this association, and the results have been highly inconsistent—eight positive and 11 negative studies (2, 12, 15–30, and unpublished data of W. Coryell). Most researchers failing to find a significant association suggested that their negative findings reflected the lack of specificity of the DST. However, no author attempted to explain why other investigators, using the same diagnostic criteria, found marked differences in nonsuppression rates between patients with endogenous and nonendogenous depression. Table 1 is a summary of the 19 studies examining the relationship between the DST and RDC endogenous depression in adult depressed patients. In the six studies in which endogenous depression was diagnosed in 50% or fewer of the patients, the DST nonsuppression rate was significantly higher in the endogenous group (53.6% versus 11.4%; Cochran-Mantel-Haenszel $\chi^2 = 110.05$, df=1, p<0.001). Investigators in 13 studies diagnosed endogenous depression in more than one-half of the patients, and in these studies DST nonsuppression was *not* significantly more frequent in the endogenous group (37.4% versus 33.7%; Cochran-Mantel-Haenszel $\chi^2 = 0.17$, df=1, n.s.). The relationship between DST result, endogenous subtype, and the ratio of endogenous to nonendogenous diagnoses was similar for the inpatient and

TABLE 1. Studies of the DST in RDC Endogenous and Nonendogenous Depression[a]

Study	Time of Blood Sampling	Threshold for Nonsuppression (μg/dl)	Inpatient or Outpatient Status	Nonendogenous Depression			Endogenous Depression		
				N	Non-suppressors N	%	N	Non-suppressors N	%
Studies in which ≤50% of patients had endogenous depression	—	—	—	334	38	11.4	194	104	53.6
Brown and Shuey (15)[b]	8:00 a.m. 4:00 p.m. 11:00 p.m.	6	Inpatient	43	7	16.3	6	4	66.7
Giles and Rush (16)[b]	4:00 p.m.	4	Outpatient	95	4	4.2	55	24	43.6
Nasr et al. (17)[b]	4:00 p.m.	5	Outpatient	26	5	19.2	14	6	42.8
D'Haenen et al. (18)[c]	8:00 a.m. 4:00 p.m. 11:00 p.m.	5	Inpatient	31	8	25.8	20	14	70.0
Sylvalahti (19)[b]	8:00 a.m. 4:00 p.m.	5	Both	123	10	8.1	83	47	56.6
Lieber and Newbury (20)[b]	4:00 p.m. 10:00 p.m.	5	Inpatient	16	4	25.0	16	9	56.3
Studies in which >50% of patients had endogenous depression	—	—	—	187	63	33.7	634	237	37.4
Caine et al. (21)[b]	4:00 p.m. 11:00 p.m.	5	Inpatient	7	5	71.4	13	5	38.5
Carroll et al. (22)[d]	4:00 p.m.	6	Outpatient	13	1	7.7	59	19	32.2
Meltzer et al. (23)[b]	8:00 a.m. 4:00 p.m.	5	Inpatient	6	4	66.7	20	6	30.0
Peselow et al. (24)[e]	4:00 p.m.	5	Outpatient	36	7	19.4	52	13	25.0
Rabkin et al. (25)[e]	4:00 p.m.	5	Outpatient	21	3	14.3	33	6	18.2
Rush et al. (26)[b]	8:00 a.m. 4:00 p.m. 11:00 p.m.	4	Both	11	1	9.1	46	22	47.8
Stokes et al. (12)[d]	8:00 a.m.	5	Inpatient	17	8	47.1	94	27	28.7
Zimmerman et al. (2)[d]	8:00 a.m. 4:00 p.m.	5	Inpatient	21	7	33.3	138	49	35.5
Alexopoulos et al. (27)[b]	8:00 a.m. 4:00 p.m. 11:00 p.m.	5	Inpatient	16	12	75.0	57	41	71.9
Dam et al. (28)[b]	8:00 a.m.	5	Inpatient	11	6	54.4	26	10	38.5
Coryell (unpublished data)[d]	4:00 p.m.	4	Outpatient	11	3	27.3	27	6	22.2
Davidson et al. (29)[e]	4:00 p.m.	5	Inpatient	9	0	0.0	40	16	40.0
Kocsis et al. (30)[b]	8:00 a.m. 4:00 p.m. 11:00 p.m.	5	Inpatient	8	6	75.0	29	17	58.6

[a]Brown and Shuey (15) used 2 mg of dexamethasone; 1 mg was used in all other studies.
[b]Report did not indicate whether patients with probable diagnoses were included in endogenous or nonendogenous group.
[c]Patients with probable diagnoses included in group with endogenous depression.
[d]Data on patients with probable diagnoses were presented separately in report but are included here with data for endogenous depression.
[e]Patients with probable diagnoses included in group with nonendogenous depression.

outpatient samples, and the studies in table 1 also did not differ in other potentially important factors, i.e., time of blood sampling and the cutoff value used to determine DST nonsuppression.

Interstudy differences in the ratio of endogenous to nonendogenous diagnoses may, of course, reflect true sample differences. It is therefore not surprising that, of the 13 studies in which more than half of the patients were diagnosed as having endogenous depression, three showed the predicted association between RDC subtype and DST result. However, different prevalences of endogenous depression may also reflect vari-

ability in the application of the criteria. As discussed elsewhere (31), this is a particularly subtle and elusive source of variance—one that is likely to go undetected because of the prevailing assumption that specified criteria ensure uniform application.

In rare cases there is a high index of suspicion of intercenter diagnostic differences because two research groups used similar assessment tools but different quantitative thresholds for determining symptom presence. For example, both Kupfer and Frank in Pittsburgh (32) and our research group in Iowa (2) specified the cutoffs on the Schedule for Affective Disorders

TABLE 2. Definitions of *DSM-III* Melancholia Criteria Used by Iowa and Pittsburgh Research Groups

DSM-III Melancholia Criterion	Iowa Definition	Pittsburgh Definition
Loss of pleasure in all or almost all activities	All or almost all activities less interesting or pleasurable (SADS item 326 score=5 or 6)	Same
Lack of reactivity to usually pleasurable stimuli (patient does not feel much better, even temporarily, when something good happens)	Patient rarely feels any better after positive environmental events (SADS item 350 score=5 or 6)	Same
At least three of the following:		
Distinct quality of depressed mood, i.e., depressed mood is perceived as distinctly different from kind of feeling experienced following death of loved one	Patient feels depressed feelings are qualitatively different from kind of feeling he would have or has had following death of loved one (SADS item 236 score≥3)	Same
Depression is regularly worse in morning	Depression at least mildly worse in morning (SADS item 351 score≥3)	Same
Early morning awakening (at least 2 hours before usual time of awakening)	Patient awakes in early hours of morning and is unable to fall asleep again (Hamilton score=2)	Patient almost always has significant difficulty staying asleep usual amount of time (beyond 5 hours of sleep), or final awakening after less than 5 hours of sleep (SADS item 272 score ≥5 and SADS item 275 present)
Marked psychomotor retardation or agitation	Obvious retardation or agitation at interview (score on Hamilton item 8 or 9≥2)	Psychomotor retardation so marked that conversation is difficult to maintain, or agitation so marked that patient is almost constantly moving about and pacing (score on SADS item 341 or 348≥5)
Significant anorexia or weight loss	Patient has loss of appetite but still may eat, or definite weight loss according to patient (Hamilton item 12 score≥1 or Hamilton item 16 score=2)	Patient has no appetite but forces self to eat or has to be fed, or weight loss of at least 15 lb (score on SADS item 318 or 319≥5)
Excessive or inappropriate guilt	Self-reproach, feelings of having let people down, ideas of guilt or rumination over past errors or misdeeds (Hamilton item 2 score≥1)	Severe, pervasive feelings of intense guilt, or generalizes self-blame to most situations (SADS item 241 score≥5)

and Schizophrenia (SADS) and the Hamilton Rating Scale for Depression used for determining the presence of *DSM-III* melancholic symptoms. A comparison of these cutoffs suggests that we diagnose melancholia more broadly than the Pittsburgh group (table 2). The inclusion of such specific information in a paper's methods section, however, is unusual.

Empirical demonstration of intercenter diagnostic differences is logistically and technically difficult. A study of interrater reliability should not be based on a videotape or joint interview approach because the way the questions are asked will influence the raters' decisions, thereby increasing the level of agreement. A test-retest design would be the most appropriate method, but it introduces patient variance as an additional cause of unreliability. Consequently, in a study of intercenter diagnostic differences it would be necessary to first obtain baseline estimates of the test-retest reliabilities of the diagnostic practices within each center before examining the test-retest agreement between the different centers.

In the present study we compared the Iowa and

Pittsburgh methods of diagnosing *DSM-III* melancholia (in which discrepancies are primarily due to differences in the cutoffs used on standardized instruments to determine symptom presence) and the Iowa and Dallas methods of diagnosing RDC endogenous depression (in which discrepancies are primarily due to differences in interpretation of criteria).

METHOD

The subjects were 60 consecutively admitted inpatients with RDC nonpsychotic major depressive disorder. The majority were female (65.0%, N=39), were high school graduates (86.7%, N=52), and had one or more prior episodes of depression (86.7%, N=52). Their mean±SD age was 38.9±15.2 years. Their mean ±SD scores on the rating scales completed during the first week of hospitalization reflected a moderate to severe level of symptoms (17-item Hamilton scale, 21.6±5.6; Global Assessment Scale, 42.6±4.5).

The subjects were interviewed by Dr. Zimmerman

TABLE 3. Definitions of RDC Criteria for Endogenous Subtype of Depression Used by NIMH Collaborative Study and Dallas Affective Disorders Clinic

RDC Criterion for Endogenous Depression	NIMH Collaborative Study Definition	Dallas Affective Disorders Clinic Definition
Guilt/self-reproach	Patient often feels somewhat guilty about past actions, such as consequences of his illness, and exaggerates their significance (SADS item 242 score≥3)	Feelings of self-deprecation or guilt involving several areas of functioning (e.g., work, parenting, marriage), recurring frequently each day and constituting prominent part of clinical picture
Psychomotor retardation	Conversation is noticeably retarded but not strained (SADS item 342 score≥3)	Observation: noticeable latency in speech, noticeably slowed physical movements; interview: significant reduction in daily activities and reports of slowing by patient and, unless patient lives alone, another person
Psychomotor agitation	Unable to sit quietly in a chair; symptom must last at least a few days (SADS item 334 score≥3)	Observation: patient unable to sit still (e.g., constantly crossing and uncrossing legs, tapping toe, shifting in chair, walking around during interview); interview: restlessness for several hours every day for at least a week and noticed by another person (unless patient lives alone)
Unreactivity	Patient rarely feels any better after positive environmental events (SADS item 350 score=5 or 6)	Dysphoria entirely unchanged by events, activities, or circumstances
Pervasive loss of interest	All activities less interesting or pleasurable (SADS item 326 score=6)	Complete loss of interest in all activities
Nonpervasive loss of interest	Several activities less interesting or pleasurable (SADS item 326 score≥3)	Complete loss of interest in several activities, or some loss in all activities
Diurnal variation, a.m. worse	Depression at least mildly worse in morning (SADS item 351 score≥3)	Mood consistently worse most mornings
Terminal insomnia	Patient often has significant difficulty staying asleep the usual amount of time (beyond 5 hours), or final awakening after less than 5 hours of sleep (SADS item 272 score≥3 and SADS item 275 present)	Final awakening at least 1 hour before normal, at least four nights per week
Decreased appetite	At least mild decrease in usual appetite (SADS item 317 score≥3)	Decreased desire for or interest in food accompanied by reduced intake
Weight loss	At least 5 lb (SADS item 319 score≥3)	Two lb/week over several weeks, 5 lb in 1 week, or 10 lb in 6 months (not due to dieting)
Distinct quality of mood	Patient feels depressed feelings are qualitatively different from kind of feeling he would have and has had after death of loved one (SADS item 236 score≥3)	Readiness to discriminate present feelings from those following a loss, and perceived difference is due to more than lack of sufficient reason or severity of symptoms

with the SADS, supplemented with questions necessary to complete the Hamilton scale. The severity thresholds used by our group and Kupfer et al. to determine the presence of individual *DSM-III* melancholic symptoms are based on the Hamilton and SADS items and are detailed in table 2. The cutoffs used by Kupfer et al. seem higher for the four items we rated on the Hamilton scale and they rated on the SADS.

We collaborated with Donna E. Giles, Ph.D., and Michael Schlesser, M.D., of the Dallas Affective Disorders Clinic to develop a semistructured interview and a set of symptom definitions corresponding to their interpretation of the RDC criteria for endogenous depression. Our definitions were largely taken from those of the NIMH-Clinical Research Branch Collaborative Program on the Psychobiology of Depression, and over the years our raters were trained by collaborative study raters. Table 3 shows that the symptom definitions used by Giles, Schlesser, and their colleagues are more restrictive than the collaborative study definitions. For example, pervasive loss of interest is scored positive by the collaborative study raters if there is *some* loss of interest in all usually pleasurable

activities, whereas Dallas interviewers require *complete* loss of interest. The Dallas definition of guilt requires that it occur frequently every day, involve several areas of functioning, and' constitute a prominent part of the clinical picture. The collaborative study convention requires only that inappropriate guilt be present. Decreased appetite is considered present by collaborative study raters if there is a mild decrease in the patient's usual appetite, whereas the Dallas raters require decreased appetite together with decreased consumption of food. The difference between the Dallas and collaborative study conventions is not simply a matter of threshold; in addition, some symptoms are defined differently. For example, terminal insomnia is defined by the collaborative study in terms of the total number of hours the patient sleeps at night (i.e., final awakening after less than 5 hours of sleep), whereas the Dallas criteria refer only to the final awakening time regardless of the number of hours of sleep. Yet another difference concerns the time period to which the patient is directed when describing the symptom. The Dallas group inquires about each symptom for the worst part of the current episode, whereas the collab-

TABLE 4. *DSM-III* Melancholia Diagnoses and Symptoms in 60 Depressed Patients Rated According to Iowa and Pittsburgh Symptom Definitions[a]

Diagnosis/Symptom	Iowa		Pitts-burgh		p[b]
	N	%	N	%	
Melancholia	18	30.0	7	11.7	<0.001
Guilt	53	88.3	4	6.7	<0.001
Terminal insomnia	25	41.7	26	43.3	n.s.
Agitation or retardation	8	13.3	0	0.0	<0.01
Decreased appetite or weight loss	39	65.0	18	30.0	<0.001

[a]Table 2 contains the Iowa and Pittsburgh symptom definitions.
[b]McNemar test, df=1, corrected for continuity.

orative study method specifies the episode nadir for only some items.

Dr. Coryell or Dr. Black administered the Dallas interview to the same 60 patients within 3 days of the SADS interview. All assessments were completed within the first week of hospitalization. The test-retest reliability of the Dallas diagnoses was examined in 20 patients, whom Dr. Zimmerman also evaluated with the Dallas interview (as a supplement to the SADS).

RESULTS

As expected, significantly fewer patients were diagnosed as having melancholia with the Pittsburgh scoring thresholds than with the Iowa thresholds (table 4). The most striking difference in symptom prevalence was for inappropriate or excessive guilt, which was judged to be present in 13 times as many patients according to the Iowa threshold. The broader Iowa definition of psychomotor change and appetite/weight loss also resulted in significantly higher frequencies of these symptoms.

The test-retest reliability of endogenous subtyping according to the Dallas interview was very good (kappa=0.74). For only two patients did one rater diagnose endogenous and the other diagnose nonendogenous depression; in the remaining three disagreements, one rater diagnosed probable endogenous depression. When the definite and probable endogenous groups were combined, which is the usual research convention, the coefficient of agreement was 0.83.

The Dallas interpretation of the RDC was significantly narrower than the collaborative study's interpretation, and four symptoms were determined to be present in significantly fewer patients (table 5).

Tables 4 and 5 show some differences in symptom frequencies between the collaborative study and Iowa ratings. These are primarily due to differences between the RDC and *DSM-III* symptom definitions. For example, psychomotor change must be "marked" according to *DSM-III* but not the RDC, and this explains the fourfold difference in prevalence. Other differences

TABLE 5. RDC Endogenous Depression Diagnoses and Symptoms in 60 Depressed Patients Rated According to Symptom Definitions Used by the NIMH Collaborative Study and Dallas Affective Disorders Clinic[a]

Diagnosis/Symptom	Collabo-rative Study		Dallas		p[b]
	N	%	N	%	
Definite endogenous	34	56.7	21	35.0	<0.05
Definite/probable endogenous	50	83.3	37	61.7	<0.01
Distinct quality of mood	33	55.0	28	46.7	n.s.
Lack of reactivity	27	45.0	25	41.7	n.s.
Diurnal variation, a.m. worse	14	23.3	14	23.3	n.s.
Pervasive anhedonia	28	46.7	22	36.7	n.s.
Guilt	44	73.3	25	41.7	<0.001
Middle or terminal insomnia	50	83.3	39	65.0	<0.05
Agitation or retardation	35	58.3	23	38.3	<0.05
Decreased appetite	38	63.3	32	53.3	n.s.
Weight loss	20	33.3	25	41.7	n.s.
Mild anhedonia	57	95.0	49	81.7	<0.05

[a]Table 3 contains the collaborative study and Dallas symptom definitions.
[b]McNemar test, df=1, corrected for continuity.

in symptom prevalence were the result of differences in rating scale operationalization; e.g., the collaborative study definition of guilt is a SADS score of 3 or higher, and the Iowa definition is a Hamilton score of 1 or higher.

DISCUSSION

During the past two decades there has been a proliferation of specified criteria for a variety of psychiatric diagnoses (33). Complementing this development have been investigations of the comparability of competing criteria sets, and these studies have shown that often there is little overlap between the systems (34–37). Even relatively contemporary criteria, which do not appear to vary greatly in their defining and exclusion criteria, demonstrate high levels of discordance (38).

The results of the present study call into question whether the major goal of the operationalization of psychiatry's diagnostic constructs, the improvement in diagnostic reliability, has in fact been achieved or even approached. It may be possible for research centers to train their own workers to agree with each other, but this in no way guarantees that workers at another center, using the same diagnostic criteria, will diagnose patients similarly. Thus, a review of reliability studies conducted during the past 10–15 years may not document problems with the reliability of psychiatric diagnoses. The fact that Kupfer et al. and our research group used different thresholds on commonly used in-

struments to determine symptom presence leaves no doubt that intercenter differences in criteria application exist.

Diagnoses, even when based on specified criteria, are nevertheless based on some level of inference, and our comparison of the NIMH collaborative study and Dallas interpretations of the RDC criteria for the endogenous subtype of depression suggest that this is a significant source of intercenter variability. The present study would have been methodologically stronger if our raters had been trained by the Dallas group, and it is possible that our reliable Dallas diagnoses are not an accurate representation of their diagnostic procedure. All we can definitely say is that we worked with the Dallas group to develop an interview reflecting their diagnostic methods, that we used this interview reliably, and that we took the diagnostic process seriously.

The problem of cross-center diagnostic differences is unlikely to be unique to research on endogenous depression. Interrater reliability studies of all psychiatric diagnoses, using raters trained at different centers, are needed. The demonstration of poor reliability raises the specter of the criticisms of psychiatric diagnosis made in the 1960s; however, a solution to the unreliability of specified criteria is not readily apparent. Perhaps the current diagnostic criteria remain too inferential and need to be defined in more precise terms, such as those illustrated in tables 2 and 3. Certainly in the area of personality disorders, where levels of diagnostic reliability have not been as high as those for axis I disorders, more precise specifications and definitions of the criteria contributed to improved reliability of diagnosis (39).

Independent replication of research is integral to the science of medicine. Therefore, when possible, authors of research articles should consider including in their methods sections explicit details of their diagnostic methods, such as the cutoffs used on standardized instruments to define symptom presence. Only because this was done by our research group and the group in Pittsburgh were we able to unambiguously identify differences in diagnostic conventions. Of course, identification of this type of variability occurs only when signs and symptoms are rated on ordinal scales, such as those included in the SADS, and not when the instrument is designed to generate dichotomous judgments.

We began this paper by noting that technological advances are proceeding at a rapid pace as researchers search for specific physical pathologies associated with psychiatric disorders. We conclude by considering the following question: If intercenter differences in diagnostic practices are a significant source of variation, and we believe that they are, to what degree will this impede efforts to identify specific biologic diagnostic markers? One possible consequence is that valid markers will be inappropriately dismissed. Diagnostic unreliability results in the misclassification of some true cases as noncases and the misclassification of some noncases as cases. Diagnostic unreliability will there-fore limit demonstration of the true diagnostic ability of some putative biologic tests. Carroll (40) has mathematically demonstrated how test sensitivity and specificity decline as a function of decreasing diagnostic reliability.

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Regional Variation in Patterns of Inpatient Psychiatric Care

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Regional variation in both average length of stay and number of beds per 100,000 population is described for inpatient psychiatric care in the United States during 1983. The greatest differences were between the Northeast and Mid-Atlantic regions, on the one hand, and the Pacific and Southwest regions, on the other. Medical centers of the U.S. Department of Veterans. Affairs (VA), whose policies are largely centrally determined, followed the same regional trends. Regional average length of stay, particularly in public sector mental health care organizations, was higher in regions with more occupied beds per 100,000 population.

(Am J Psychiatry 1990; 147:1180–1183)

S urveys of general hospital utilization (1, 2) have revealed substantial regional differences in total hospital days per capita and in average length of stay, especially between the northeastern and western regions of the country. In the course of developing monitors to aid practitioners reviewing psychiatric quality of care data within the U.S. Department of Veterans Affairs (VA) health care system, we noted substantial variation in the average length of stay among different regions of the country. In view of the high level of concern about the cost and quality of health care (3–5), an appreciation of regional practice variation and an understanding of the basis for such variation are important to the development of rigorous and legitimate standards of care. To clarify the magnitude and reasons for regional variation in psychiatric length of stay, we sought to identify patterns of regional variation in the VA medical system, to compare these patterns with those found in each of four other types of mental health care organizations, and to identify possible reasons for the regional variation.

BACKGROUND

Examination of regional variation in medical practice has stimulated important questions about the relative appropriateness and quality of care in different areas of the country (1, 2). Previous studies of variation in psychiatric care have explored differences across types of mental health care organizations, e.g., general hospitals versus state hospitals (6), and differences associated with different payment structures (7). While geographic variation has been accounted for in the analysis of large data sets (8), to our knowledge the issue of geographic variation in psychiatric care has not been explicitly explored.

The psychiatric component of the VA health care system is the largest integrated mental health system in the United States. Because it is a national system with internally uniform administrative regulations and management practices, psychiatric practice in the VA could be expected to be relatively independent of local influences and thus resistant to practice variations observed in other mental health care organizations.

A major concern in the study of regional variation is the extent to which such variation mirrors differences in socioeconomic and health status variables in different regions of the country (1, 2). VA medical centers are distinctive in that they serve a relatively homogeneous population. Eligibility for services is limited to veterans of the U.S. armed forces, and service access priorities are uniformly determined according to national disability standards and income criteria. As a consequence of these administrative service priorities, VA psychiatric patients across the country can be assumed to be more homogeneous than patients in most other health care systems. This presumed administrative and demographic homogeneity lends special interest to the question of whether the patterns of care in the VA follow regional patterns of care in other mental health care organizations.

METHOD

The principal source of data for this report was the 1983 biennial inventory of specialty mental health care organizations, conducted by the Survey and Reports Branch, Division of Biometry and Applied Sciences, National Institute of Mental Health (6). This survey collects and synthesizes data from each state and the

FIGURE 1. Seven VA Administrative Regions
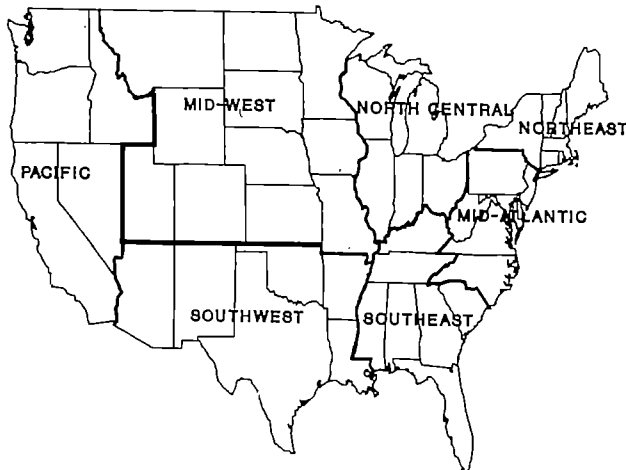
District of Columbia on each of five types of mental health care organizations: 1) state and county mental hospitals (N=280), 2) multiservice mental health care organizations (including but not limited to community mental health centers) (N=649), 3) private psychiatric hospitals (N=221), 4) psychiatry services in nonfederal general hospitals (N=1,259), and 5) psychiatry services in VA medical centers (N=125).

The NIMH survey data that form the basis of this report include 1) the number of psychiatric beds occupied at the end of 1983 (N=262,673), 2) the total number of episodes of care (discharges plus patients remaining at the end of the year) (N=1,860,613) delivered during 1983, and 3) the total bed-days of care delivered during 1983 (N=81,821,000). These data were combined with data on the total civilian population of each state (6) and on the veteran population of each state (9) to determine 4) the number of occupied psychiatric beds per 100,000 population, and 5) the number of episodes of care delivered per 100,000 population. Finally, 6) the average length of stay per episode of care was calculated (the total days of care divided by the number of episodes of care, truncated at 365 days). Regional boundaries were adapted from the seven VA administrative regions (figure 1), and data were pooled by region. For VA care, the number of occupied beds per 100,000 population and the number of episodes of care delivered per 100,000 population were calculated on the basis of the 1983 veteran population of the states in each region (9).

RESULTS

Average Length of Stay

Table 1 presents the average length of stay per episode of care for each type of organization and all non-VA organizations combined for each region. There were significant differences in average length of

stay across regions (F=2.58, df=6, 24, p<0.05). Specifically, there was a significant difference between the Mid-Atlantic and Northeast regions, on the one hand, and the Mid-West, Pacific, and Southwest regions, on the other (p<0.05, Duncan's multiple range test). The longest average lengths of stay, for both VA and the combined non-VA mental health care organizations, were in the Northeast and Mid-Atlantic regions (all over 50 days); they were more than 20% higher than the corresponding figures for the entire nation. In the VA system, the shortest lengths of stay were in the Pacific and Southwest regions, respectively 12% and 23% below the national average for the VA. Among non-VA organizations taken together, two of the three shortest lengths of stay were also in the Pacific and Southwest regions and were 29% and 12% below the average length of stay for the entire nation (table 1).

Among specific types of non-VA mental health care organizations, these regional differences in average length of stay were most clearly evident for state and county mental hospitals, while they were discernible but less pronounced for multiservice mental health centers. There was little difference for private hospitals and virtually none for nonfederal general hospitals (mean±SD=15±2 days, range=12–18 days).

Correlation coefficients were calculated to illustrate the relationship between the regional average lengths of stay in the different types of mental health care organizations. These correlations revealed significant associations between the regional lengths of stay in the VA and the aggregated non-VA organizations (r= 0.76, df=5, p<0.05) and, more specifically, between the regional lengths of stay in the VA and both state and county mental hospitals (r=0.79, df=5, p<0.04) and multiservice mental health centers (r=0.73, df=5, p<0.10).

Other Variables

The lower part of table 1 contains data on the number of occupied psychiatric beds per 100,000 population in each type of organization in each region. Regional differences reached only marginal statistical significance (F=2.06, df=6, 24, p<0.10). The highest numbers of non-VA psychiatric beds were in the Northeast and Mid-Atlantic regions (136 and 109, respectively), while the lowest numbers were in the Pacific and Southwest regions (48 and 59). This pattern of regional variation was partially mirrored in the VA, most clearly for the Pacific and Southwest regions, which had the lowest numbers of occupied VA psychiatric beds per 100,000 population (43 and 59, respectively).

No consistent differences between regions were identified for the number of episodes of care per 100,000 population (raw data available on request).

Comparison of regional variation in average length of stay and in number of occupied beds per 100,000 persons suggests that the longer lengths of stay in the Northeast and Mid-Atlantic regions may be related to

TABLE 1. Average Length of Stay and Number of Occupied Beds During 1983 in VA and Non-VA Mental Health Facilities in Each VA Administrative Region[a]

Region[b]	VA Medical Centers	Non-VA Facilities				
		Total	State/ County Mental Hospitals	Multiservice Mental Health Centers	Private Psychiatric Hospitals	Nonfederal General Hospital Psychiatry Services
Average length of stay/ episode (days)						
Total	43	41	92	39	33	15
Mid-Atlantic	56	50	124	67	31	14
Northeast	54	61	127	58	44	16
Mid-West	48	33	72	30	51	15
North Central	41	36	69	51	28	18
Southeast	39	39	82	28	29	15
Pacific	38	29	96	22	27	12
Southwest	33	36	62	35	44	16
Occupied psychiatric beds at the end of 1983/ 100,000 population[c]						
Total	72	82	51	10	7	14
Mid-Atlantic	75	109	69	16	10	14
Northeast	86	137	99	11	9	18
Mid-West	112	66	41	5	3	17
North Central	61	69	39	7	5	18
Southeast	84	80	50	11	8	11
Pacific	43	49	26	8	6	9
Southwest	59	60	31	11	8	10

[a]Based on NIMH survey data (6).
[b]Regions listed in descending order of VA lengths of stay.
[c]VA occupied beds=beds/100,000 veterans.

the greater numbers of occupied beds there and that the shorter lengths of stay in the Pacific and Southwest regions are associated with a smaller number of beds per 100,000 persons (table 1). To further examine these associations, we combined all VA and non-VA mental health care organizations and calculated the correlation between average length of stay and number of occupied beds per 100,000 population across the seven regions. The two variables proved to be highly correlated (r=0.99, df=5, p<0.01). The overall number of psychiatric beds per 100,000 was also correlated with average length of stay in VA facilities (r=0.85, df=5, p<0.02), state and county mental hospitals (r= 0.82, df=5, p<0.03), and multiservice mental health centers (r=0.75, df=5, p<0.06). The correlation of number of beds and length of stay across regions was not significant for private psychiatric hospitals or nonfederal general hospitals.

DISCUSSION

For non-VA mental health care organizations considered together, the longest lengths of stay during 1983 were in the Northeast and Mid-Atlantic regions, and the shortest lengths of stay were in the Pacific, Mid-West, and Southwest regions. The highest numbers of non-VA psychiatric beds were also in the Northeast and Mid-Atlantic regions, and the lowest

numbers were in the Pacific and Southwest regions. For the most part, psychiatric care provided by the VA followed the patterns identified for non-VA organizations, particularly those observed for state and county mental hospitals. Average length of stay in the VA health care system across regions correlated significantly with the average length of stay for non-VA organizations. In view of the assumption of relatively small differences in the clinical and sociodemographic characteristics of those eligible for VA care in different regions of the country, these differences can not be readily attributed to regional variations in clinical need.

It appears that average length of stay is strongly influenced, at least in public sector organizations, by the number of psychiatric beds available in each region. In our analysis, regional lengths of stay in VA medical centers and in state and county mental hospitals were strongly correlated with the number of occupied beds for all organizations taken together.

In his review of mental health policy in California, Lerman (10) showed that the number of inpatient psychiatric beds reflects a broad range of political, economic, social, and professional forces. Patterns of regional variation similar to those we have described have also been identified (1, 2) for patients in the general medical sector. It is thus possible that patterns of public psychiatric care may be strongly influenced by the availability of beds, either because of trends set in the general medical sector or because of the influence

of similar extraprofessional political, social, and economic forces.

It is notable that the particular organizations in which average length of stay was significantly correlated with the number of available beds were public sector organizations (VA medical centers and state and county mental hospitals) and that the group of organizations which showed a marginal correlation between availability of beds and length of stay (multiservice mental health centers) also largely serves public sector patients. It may be that the overall number of beds in each region has the strongest impact on length of stay in institutions which serve the poor and chronically mentally ill. Private psychiatric hospitals and nonfederal general hospital psychiatry services, in contrast, seem to operate more independently of overall regional availability of beds. Such hospitals have traditionally been able to shape and select their patient populations and patterns of practice through admissions policies that permit referral of many disabled, violent, and poor patients to public facilities.

A plausible interpretation of these data is that the needs of the chronically mentally ill are so extensive that in the presence of resources for longer stays, more extensive hospital treatment will be prescribed. The question of whether longer stays are either clinically beneficial or medically necessary goes beyond the data under review here. It should be noted, however, that in some western states fewer hospital beds may be necessary and shorter stays may be possible because of the existence of an extensive network of community care facilities targeted to the needs of those at highest risk of hospitalization (10, 11).

To more fully understand the relation of these data to the utilization of public sector hospitals, the impact of a number of additional factors would need to be considered: age, climate, regional psychiatric epidemiology, and community resources (e.g., safe and affordable housing, transitional facilities, poverty levels, urban crowding). Therefore, although distinct regional patterns of inpatient psychiatric care can be discerned and seem to be influenced, particularly in the public sector, by the availability of beds, the ultimate importance of such regional patterns to the care of psychiatric patients can not be determined without further information on regional health care needs and on the full spectrum of available mental health and social services. Our description of significant regional variation in psychiatric inpatient care, however, does suggest that any nationally applicable clinical standards or guidelines must take into account existing patterns of regional variation.

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Relation of Clinical Variables
to Dissociative Phenomena in Eating Disorders

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In this study 30 female patients with eating disorders were compared with 30 age-matched normal female subjects. The patients demonstrated significantly higher levels of dissociative psychopathology than the comparison subjects. Furthermore, the presence of severe dissociative experience appeared to be specifically related to a propensity for self-mutilation and suicidal behavior. These findings are discussed in light of recent data which suggest that neurochemical systems shown to be abnormal in patients with eating disorders may be key pathophysiologic substrates for dissociative experience.
(Am J Psychiatry 1990; 147:1184–1188)

D issociation is a complex psychobiological process that exists along a continuum from such normal experiences as daydreaming and transient lapses in attention to a pathological failure to integrate thoughts, feelings, memories, and actions into a coherent and unified sense of consciousness (1–3). These latter, extreme forms of dissociative experience are characterized by severe disturbances in memory (typically, amnesias) and disturbances in the sense of self, exemplified in the alter identities of multiple personality disorder, the self-annihilation of depersonalization disorder, and the loss of autobiographical memories in psychogenic amnesia.

Pierre Janet, at the turn of the century, was the first investigator to systematically study the process of dissociation (in patients with hysteria). Janet demonstrated that dissociation plays an important defensive role in coping with traumatic experiences (4). Modern interest in dissociation has been sparked by the increasing recognition of multiple personality disorder

and other dissociative sequelae of child abuse (5). Ludwig (6) has outlined a number of important defensive functions that dissociation provides for the individual, including 1) automatization of behavior, 2) resolution of irreconcilable conflicts, and 3) escape from the constraints of reality. Most contemporary theories emphasize the initially adaptive and defensive role played by dissociation during acute trauma. However, this process emerges as maladaptive if it generalizes to stressful events outside of the trauma context (5, 7).

Our interest in the contribution of dissociation to the psychopathology of eating disorders was prompted by our evaluation of two patients on our unit who concurrently met the criteria for anorexia nervosa and multiple personality disorder. A review of the literature further revealed several lines of evidence to support the hypothesis of a relation between dissociation and eating disorders. First, there are reports of increased hypnotizability—a strong correlate of dissociative disorders—in patients with eating disorders (8, 9). Second, as in the treatment of dissociative disorders, hypnosis has been reported to be useful in the treatment of some eating disorder patients (10). Third, there is increasing evidence of traumatic antecedents, primarily childhood sexual abuse, in a substantial percentage of patients who have eating disorders (11–16). Fourth, there are case reports of dissociative states in eating disorder patients (17, 18), and, conversely, there is a relatively high incidence of eating disorders and gastrointestinal symptoms in patients with dissociative disorders (19–21). Finally, a review of the early clinical descriptions of patients with "hysteria" reveals that many of these cases were characterized by significant gastrointestinal symptoms, including weight loss, anorexia, and chronic vomiting.

We postulate that in patients with eating disorders, a greater capacity for dissociation may result in a narrowing of cognitive focus and the exclusion of pertinent, often conflicting, material from conscious awareness. This, together with the disturbances of self characteristic of the dissociative disorders, may account in part for the ability of patients with eating disorders to maintain the illogical distortions of thought and body image characteristic of their illness. In the present study we sought to establish whether dissociative phenomena are evident in a significant

proportion of patients with eating disorders and to characterize the associated clinical phenomenology of these patients.

METHOD

Thirty female patients consecutively admitted to the Unit on Eating Disorders in the Clinical Center of the National Institutes of Health were included in this study. All patients met the *DSM-III-R* criteria for either anorexia nervosa (N=12) or bulimia nervosa (N=18). The mean±SD age of the patient group was 23.3±4.4 years (range=16–39); the age of the anorexic patients was not different from that of the bulimic patients (23.5±6.6 and 23.1±2.9 years, respectively). The anorexic subjects were underweight at the time of the study (mean±SD=62.8%±5.5% of population average body weight), whereas all of the bulimic subjects were within ±20% of population average body weight (91.4%±10.6%). A group of 30 age-matched normal women served as a comparison group for the study. Their mean±SD age was 22.8±4.3 years (range=17–38). The comparison subjects were recruited by advertisement from the Washington, D.C., area and were free of current or past history of psychiatric illness. Matching was pairwise and was successful to within 2 years of age for each patient and her comparison subject.

Dissociative capacity was assessed with the Dissociative Experiences Scale (3, 22), a previously validated 28-item visual analogue rating scale. The response format for each item on the scale consists of a 100-mm line with no divisions that is numerically anchored at the end points. The subject is asked to indicate a response by making a slash across the line at the appropriate place. Each item score is determined by measuring the subject's slash mark to the nearest 5 mm from the left-hand anchor point. The total score is the average of the 28 item scores. Three subscale scores have also been determined on the basis of a factor analysis of the Dissociative Experiences Scale (23). The factor subscales have been shown to have construct validity for 1) psychogenic amnesia, 2) depersonalization/derealization, and 3) absorption. Additional self-report measures, including the State scale of the State-Trait Anxiety Inventory (24), the Beck Depression Inventory, and the Barrett Impulsivity Scale (25), were used. In addition, information on length of eating disorder, number of previous psychiatric hospitalizations, history of suicide attempts and self-mutilation, and history of stealing was obtained at the initial clinical interview. Finally, all patients underwent 4 consecutive days of 24-hour urine sample collections to ascertain urinary free cortisol levels concurrent with the psychological ratings.

Since previous analyses have shown that scores on the Dissociative Experiences Scale are not normally distributed, all data from the scale were analyzed with standard nonparametric statistical methods as appro-

TABLE 1. Median Total and Subscale Scores on the Dissociative Experiences Scale for Patients With Eating Disorders and for Normal Subjects[a]

	Median Score on the Dissociative Experiences Scale			
Group	Total Scale	Amnesia Subscale	Depersonalization/ Derealization Subscale	Absorption Subscale
Eating disorder patients (N=30)	16.7[b]	18.7[c]	5.3[d]	25.4[e]
Anorexic (N=12)	19.5[f]	17.3	6.4	33.1
Bulimic (N=18)	16.6[g]	18.7	5.2	21.8
Normal subjects (N=30)	6.4	3.0	2.2	12.7

[a]Statistics indicate significant differences from the group of normal subjects, Wilcoxon matched-pairs signed ranks test.
[b]$z=3.49$, df=29, p<0.01.
[c]$z=4.73$, df=29, p<0.01.
[d]$z=2.67$, df=29, p<0.01.
[e]$z=3.24$, df=29, p<0.01.
[f]$z=2.35$, df=11, p<0.02.
[g]$z=2.85$, df=17, p<0.01.

priate. Matched pairwise comparisons were done with the Wilcoxon signed-ranks test, and the Spearman rank-order correlation coefficient was used to assess degree of association. Since our hypothesis predicted a greater level of dissociative experience in the patient groups, we used one-tailed tests of significance throughout. Because urinary free cortisol measures are normally distributed data, an unpaired t test was used to compare the patient groups on this variable.

RESULTS

Summary data for median Dissociative Experiences Scale total and subscale scores for the patients and the normal comparison subjects are presented in table 1. Median total scores for the entire group of eating disorder patients and for the anorexia nervosa and bulimia nervosa groups separately were significantly higher than those for the matched normal subjects (figure 1). Within the eating disorder group, the anorexic patients had higher median total and subscale scores than the bulimic patients, except on the amnesia subscale, although the differences between these two groups were not significant.

Previous studies have shown that Dissociative Experiences Scale scores of 30 or greater reflect significant levels of dissociative psychopathology (3, 21, 22). Consistent with this finding, in our normal comparison group, all subjects had scores less than 30, and 24 of the 30 individuals had scores less than 10. Therefore, we used a Dissociative Experiences Scale score of 30 or higher to indicate a severe level of dissociative experience and a score of less than 30 to indicate dissociative

FIGURE 1. Scores of Patients With Eating Disorders and of Matched Normal Subjects on the Dissociative Experiences Scale

TABLE 2. Median Total and Subscale Scores on the Dissociative Experiences Scale for Patients With Eating Disorders Who Had Total Scores ≥30 or <30 and for Normal Subjects[a]

Group	Median Score on the Dissociative Experiences Scale			
	Total Scale	Amnesia Subscale	Depersonalization/ Derealization Subscale	Absorption Subscale
Total score ≥30				
Patients (N=9)	62.9[b]	69.1[b]	40.6[b]	70.5[b]
Matched normal subjects (N=9)	8.4	4.6	2.8	14.1
Total score <30				
Patients (N=21)	14.7[c]	8.6[d]	3.7	18.1
Matched normal subjects (N=21)	6.3	2.7	1.7	11.8

[a]Statistics indicate significant differences from the matched normal subjects, Wilcoxon matched-pairs signed ranks test.
[b]$z=2.67$, $df=8$, $p<0.01$.
[c]$z=2.14$, $df=20$, $p<0.04$.
[d]$z=3.32$, $df=20$, $p<0.01$.

experience within the normal range. Summary data for median total and subscale scores of the patients who scored outside the normal range of dissociative experience and the patients who scored within the normal range are presented in table 2. It is notable from this comparison that even the patients classified within the normal range manifested significantly higher total and subscale scores on the Dissociative Experiences Scale than the matched normal subjects, suggesting that the presence of greater dissociative capacity is a ubiquitous phenomenon with a spectrum of severity in patients with eating disorders. (The patients with severe levels of dissociative experience were not disproportionately represented by a single diagnostic type of eating disorder.)

The patients whose scores lay outside the normal range had a significantly higher frequency of suicide attempts and self-mutilation (N=9: seven self-harmful patients and two with no history of self-harm) than the patients with scores in the normal range (N=21: seven self-harmful and 14 with no history of self-harm) (p=0.03, Fisher's exact test). On the other hand, the patients with more severe levels of dissociative experience did not differ significantly from the remaining patients on overall measures of impulsivity as reflected by scores on the Barrett scale, on history of stealing, or

on measures of chronicity or severity of illness, such as age, percent of population average body weight, number of years ill, or number of previous psychiatric hospitalizations.

Using a score of 21 or greater on the Beck inventory to indicate severe depressive symptoms and a score of 20 or less to indicate mild symptoms, we found no significant relation (Fisher's exact test) between severity of depression and suicidal or self-harm behavior (Beck score≥21, N=20: nine self-harmful patients and 11 with no history of self-harm; Beck score≤20, N=8: three self-harmful and five with no history of self-harm). However, degree of affective dysphoria was correlated with level of dissociative capacity as evidenced by a significant positive relation between the Dissociative Experiences Scale score and the anxiety score ($r_s=0.36$, $df=27$, $p<0.05$) and the Beck depression scale ($r_s=0.44$, $df=26$, $p<0.03$) in the whole group of patients. Mean±SD urinary free cortisol levels, as expected, were higher in anorexic patients than in bulimic patients (66.8±8.4 μg/24 hours and 40.9 ±4.3 μg/24 hours, respectively; unpaired t test, t= 2.98, df=27, p=0.006). However, there was no relation between urinary free cortisol levels and scores on the Dissociative Experiences Scale in the group of patients as a whole.

DISCUSSION

In this study, female patients with anorexia nervosa and bulimia nervosa showed a significantly greater incidence of dissociative phenomena than a group of

age-matched normal female subjects. Further, when the patient group was divided into a subgroup with Dissociative Experiences Scale scores well outside the normal range and a subgroup with scores within the normal range, a significantly higher incidence of self-harm was noted in the patients who manifested severe dissociative experience. Interestingly, this greater incidence of self-harm did not appear to reflect a generally greater level of impulsivity, as these same patients did not differ in scores on the Barrett scale from those with scores within the normal range, nor did they report a greater number of stealing episodes. The greater self-harm in these patients also did not appear to reflect generally greater illness chronicity or severity, as the two patient groups were not significantly different in terms of age, percent of population average body weight, number of years ill, or number of previous hospitalizations. Finally, the absence of a significant relation between affective dysphoria, as reflected in Beck inventory scores, and self-harmful behavior suggests that self-destructive behavior bears a specific relation to the presence of dissociative symptoms rather than simply indicating the patients' nihilistic view of themselves and their world, which may be expected in severe depression.

Dissociation serves as an adaptive and defensive mechanism for the individual, especially in the context of sustained or repeated trauma such as incest (5, 6). In this regard, it is known that adult patients with major dissociative psychopathology have a high incidence of severe childhood abuse (5). Recent data indicating a similarly high rate of childhood abuse in eating disorder patients (11) suggest that a substantial percentage of these patients are at risk for considerable concurrent dissociative psychopathology. In addition, certain behavioral traits that characterize patients with eating disorders, such as severe food restriction, repeated periods of binge eating and purging, and repeated bouts of self-harm, may also serve as profound physiologic stressors, which may in turn alter the patients' conscious state or serve as contextual cues for induction of dissociative states, and in so doing perpetuate or enhance the propensity of the patients to dissociate.

The potentially mutually reinforcing nature of the adaptive functions of dissociation and behavioral traits that foster the presence of dissociated states of consciousness may play a role in the profound resistance to change of these maladaptive behavioral patterns. In addition, the frequently described rapid fluctuations in mood state seen in patients with eating disorders (26) may be related to the rapid alterations in state of consciousness brought on by the greater use of dissociation by the individual.

In addition to providing a context for understanding the distortions of self- and body image experienced by patients with eating disorders, we speculate that the greater propensity of eating disorder patients to undergo considerable dissociative experiences may provide some clues regarding the underlying neurobiology of dissociative events. For example, recent data suggest

that functional alterations in the activity of the endogenous opiate system and the serotonergic system may play important roles in the pathophysiology of dysphoric mood (27) and dissociative states (28, 29) as well as serve as important pathophysiologic underpinnings of the appetitive abnormalities which characterize the eating disorders (30, 31). An appraisal of the level of dissociative symptoms in patients with eating disorders may begin to allow a characterization of neurobiological abnormalities that may cluster in this subgroup of patients.

In summary, the level of dissociative experience reported by our patient groups suggests that this process may play a significant role in the adaptation to previous trauma and the presenting psychopathology of patients with eating disorders. In addition, an awareness of the presence of dissociative symptoms in eating disorder patients may have an impact on the pharmacologic and nonpharmacologic treatment and overall clinical course of these patients.

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Time-Related Predictors of Suicide in Major Affective Disorder

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The authors studied 954 psychiatric patients with major affective disorders and found that nine clinical features were associated with suicide. Six of these—panic attacks, severe psychic anxiety, diminished concentration, global insomnia, moderate alcohol abuse, and severe loss of interest or pleasure (anhedonia)—were associated with suicide within 1 year, and three others—severe hopelessness, suicidal ideation, and history of previous suicide attempts—were associated with suicide occurring after 1 year. These findings draw attention to the importance of 1) standardized prospective data for studies of suicide, 2) assessment of short-term suicide risk factors, and 3) anxiety symptoms as modifiable suicide risk factors within a clinically relevant period.

(Am J Psychiatry 1990; 147:1189–1194)

One of the most difficult challenges facing clinicians is the prevention of suicide by their patients. Since psychiatric clinicians routinely deal with patients whose diagnoses are associated with a high risk for suicide, the problem of suicide risk assessment and intervention is always a high priority.

Many of our clinical guideposts for distinguishing high-risk patients who commit suicide from the majority of patients have emerged from retrospective studies (1–5). Because of the statistical requirements for larger sample sizes, follow-up mortality studies of suicide usually encompass long intervals; to our knowledge, there are no prospective short-term (1 year) studies of suicide. Most available knowledge concerning risk factors for suicide is based on examining long-term risk (4, 5). Moreover, most studies of suicide with samples large enough for generalization have been retrospective. These retrospective studies have the disadvantage of not allowing for standardized clinical assessments.

They were unable to control for the presence of disorder-specific symptoms (i.e., depression, alcoholism, or schizophrenia) that formed the context of the suicide. The retrospective studies also introduce a tendency for hindsight bias in assessing risk because it is known that a suicide occurred. For instance, the fact that a person committed suicide may influence the perceptions of family members concerning the victim's behavior just before death. Another important dimension difficult to measure retrospectively is the time that passed between the clinician's awareness of risk factors and suicide (6).

Ideally, characteristics predicting suicide will identify short-term risk so that life-saving interventions can be made. Characteristics predicting suicide at some time in the distant future may be of relatively secondary importance because they do not define an acute emergency and may even obscure the more acute predictors that indicate something must be done immediately (7, 8).

This report represents an extension of previous work looking at prospective predictors of suicide in a sample of 954 patients with diagnoses of major affective disorders who were admitted to the Collaborative Program on the Psychobiology of Depression (9). The initial report presented a univariate analysis of characteristics of 25 patients who died by suicide over a 4-year follow-up period (10). The current report describes a multivariate analysis of patient characteristics that correlated with the outcome of suicide in our sample over 10 years. We found that discriminant function profiles predicting suicide for the first year of follow-up did not significantly predict suicide over the next 4 years. This led us to investigate the possibility that different characteristics may be observed in patients who are going to commit suicide within 1 year of initial assessment, in contrast to features observed in patients who are going to commit suicide 2–10 years after clinical assessment.

METHOD

Subjects and Procedure

The sample consisted of 954 subjects from the Collaborative Study on the Psychobiology of Depression who met Research Diagnostic Criteria (RDC) for a

major affective disorder (9). The study took place at five university centers, where, on admission to the study, all patients were assessed at intake by professional clinical interviewers using the Schedule for Affective Disorders and Schizophrenia (SADS) (11), which included the symptom variables used in the study. The sample included 401 men and 553 women. Their mean age at the time of admission to the study was 38.1 years (range=17–79), and all of the patients were Caucasian. Of the 954 patients, 569 had unipolar depression (210 with first episodes and 359 with recurrent episodes), 185 had bipolar type I, 114 had bipolar type II, and 80 had schizoaffective disorder (46 bipolar and 34 depressed); in addition, six patients had minor depression.

All patients who completed suicide during the first 10 years of the study were included. The median age of the patients who committed suicide was 36 years (range=21–73). Treatment of all study patients was administered independent of the study and in usual settings by professionals (privately or in a clinic setting). Treatment was not controlled but was recorded during follow-up visits at 6-month intervals over the 10 years.

Statistical Analysis

The study began taking in patients in January 1978. In 1982, an exploratory discriminant function analysis was performed to compare the symptoms of patients who had committed suicide or made serious attempts with those of patients who had not demonstrated any suicidal activity. The suicide group studied (N=68) included some patients who had committed suicide or made serious attempts during the index episode before entry into the study. The comparison group was matched in age, sex, and marital status.

The stepwise analysis (which assumed homogeneous variance-covariance matrixes) examined 46 symptom variables hypothesized by three of us (J.F., W.A.S., and D.C.C.) to be associated with suicidal behavior. Twelve of these were found to be effective discriminators.

Because our sample of patients who had committed suicide was small and results of discriminant function analysis are often difficult to replicate, these results were sequestered to await a cross-validation. The inevitable occurrence of more suicides allowed us to determine whether the original 1982 discriminant function predicted subsequent suicides among the surviving patients. In 1986 the discriminant function was applied to the sample to test whether the function could identify a second group of 11 patients who had committed suicide during the first 5 years of the follow-up. In the original 1986 discriminant function analysis samples, 12 of the 14 suicides had occurred within the first year. In the cross-validation sample of 11 more suicides, only one occurred within the first year of follow-up. The original 1982 discriminant function analysis did not predict suicides in the cross-validation

sample, which led to the question of whether the instability of the discriminant function was attributable to the fact that most suicides in the initial suicide group in the discriminant function analysis occurred within the first year of follow-up but the opposite was true of the suicides in the cross-validation group.

To test that hypothesis, the data were re-analyzed in 1990 with all 32 suicides divided into two groups reflecting time of suicide. The 13 suicides that occurred within the first year of follow-up were considered short-term suicides, and the 19 suicides that occurred after the first year of follow-up were considered long-term suicides.

We then compared the characteristics of both groups of patients who had committed suicide with those of the patients who had not committed suicide. The 12 characteristics examined (hopelessness, severity of hallucinations, alcohol abuse, panic attacks, loss of interest or pleasure [anhedonia], somatic anxiety, excessive bodily concern, fatigue, phobia, antisocial behavior, subjective stress, and nonreactivity) were drawn from the 1982 discriminant function analysis.

A Kruskal-Wallis analysis of variance (ANOVA) of ranks was used to evaluate the differences between groups because the symptom data exhibited heterogeneous within-group variances and a questionable distributional form that would invalidate a parametric one-way ANOVA. Two characteristics—suicidal ideation detected by the clinical rater and a history of previous suicidal behavior from the SADS interview—were added to this analysis because of their common association with suicide in previous studies, despite the fact that they did not emerge in our previous univariate analyses. Because of the emergence of somatic anxiety and panic attacks in our discriminant function analysis, the SADS item of psychic anxiety was also added to subsequent analyses to explore the possible significance of all anxiety-related items. The presence versus absence of panic attacks in the current episode among short-term and long-term suicide groups and patients who had not committed suicide was compared by chi-square test.

A series of Mann-Whitney U statistics were subsequently applied to compare each of the two suicide groups (short-term and long-term) with the patients who had not committed suicide. These U statistics test pairwise comparisons between each of the suicide groups and the patients who had not committed suicide.

Because the analyses for this study took place over a period of 8 years, new suicides in the sample were reported as the analysis progressed. Thus, we have 14 suicides in the first analysis, 25 in the second, and 32 in the third. These analyses were performed several years apart, and we learned of new suicides occurring in each interval. Instead of examining only the first sample of 14 or the second of 25, we decided that it was most sensible to include any additional suicides in each set of analyses.

TABLE 1. Chi-Square Statistics for the Kruskal-Wallis ANOVA of Ranks for 954 Patients With Major Affective Disorder Who Did or Did Not Commit Suicide

Symptom	Chi-Square		ANOVA	
	χ^2 (df=2)	p	F (df=2, 951)[a]	p
Hopelessness	7.79	0.020	2.34	0.097
Alcohol abuse	5.73	0.057	2.43	0.089
Loss of interest or pleasure (anhedonia)	8.79	0.012	3.74	0.035
Psychic anxiety	6.36	0.042	3.27	0.038
Suicidal ideation	4.48	0.106	2.10	0.123
Suicide attempts	3.03	0.220	1.90	0.150
Obsessive-compulsive features	4.57	0.102	2.97	0.052
Indecisiveness	6.34	0.042	3.57	0.029
Diminished concentration	7.84	0.020	3.11	0.045
Global insomnia	6.58	0.037	2.39	0.096

[a]For suicidal ideation, df=2, 950.

TABLE 2. Probability Values for Mann-Whitney U Statistics Comparing 954 Patients With Affective Disorder Who Committed Suicide Within 1 Year (Short-Term) or 2-10 Years (Long-Term) and Patients Who Did Not Commit Suicide

Symptom	Short-Term Suicide p	Long-Term Suicide p
Hopelessness	0.463	0.007
Alcohol abuse	0.029	0.372
Loss of interest or pleasure (anhedonia)	0.005	0.223
Psychic anxiety	0.012	0.879
Suicidal ideation	0.613	0.041
Suicide attempts	0.815	0.086
Obsessive-compulsive features	0.063	0.303
Indecisiveness	0.085	0.062
Diminished concentration	0.028	0.078
Global insomnia	0.011	0.765

RESULTS

Thirty-two (3%) of the 954 patients had committed suicide. Thirteen (41%) of these suicides occurred during the first year of follow-up: three (9%) during the first 3 months and seven (22%) during the first 6 months. Nineteen (59%) of the suicides occurred during follow-up years 2–10.

Previously reported univariate analyses (10) showed that no specific RDC type or subtype of major affective disorder had a significantly higher incidence of suicide than any of the others.

The 1982 discriminant function analysis that selected the 12 characteristics of hopelessness, severity of hallucinations, alcohol abuse, panic attacks, loss of interest or pleasure (anhedonia), somatic anxiety, excessive bodily concern, fatigue, phobia, antisocial behavior, subjective stress, and nonreactivity produced a Wilks's lambda of 0.71 (p=0.05) and a canonical correlation of 0.54. It correctly classified 13 (93%) of the 14 suicides despite a relatively high false-positive rate (41%). It also correctly classified 27 (50%) of the 54 nonlethal suicide attempts and 28 (41%) of the 68 patients who did not attempt suicide. The function failed, however, to predict the suicides and suicide attempts that occurred primarily during years 2–5 of the follow-up at better than chance expectation. It correctly classified seven (64%) of the 11 suicides, 53 (66%) of the 80 nonlethal attempts, and 446 (56%) of the 800 patients who did not attempt suicide.

Table 1 shows the results of the ANOVA of seven of the predictive symptoms of suicide plus suicide attempts, suicidal ideation, and psychic anxiety in patients who committed suicide within 1 year after assessment, patients who committed suicide in 1–10 years, and patients who did not commit suicide. There were significant differences among the three groups in many of the symptoms. The results of the Mann-Whitney U statistics comparing the two groups of patients who had committed suicide with the patients who had

not committed suicide are given in table 2. Symptoms that were significantly more severe among those who committed suicide within 13 months than among those who did not commit suicide were loss of interest or pleasure (anhedonia), psychic anxiety, obsessive-compulsive features, global insomnia, and alcohol abuse.

The symptom (not the disorder) of panic attacks was present at the intake SADS evaluation in eight (62%) of 13 patients who committed suicide within 1 year but only 262 (28%) of 922 patients who did not commit suicide and four (21%) of the 19 patients who committed suicide in 2–10 years. Despite the small number of suicides overall, this result cannot be attributed to chance alone (χ^2=7.43, df=2, p=0.024). These data suggest that the presence of panic attacks may be another risk factor in short-term suicide (within a year of assessment).

Suicidal ideation, hopelessness, and history of suicide attempts were not significantly associated with short-term suicide but were significantly (or nearly significantly in the case of attempts) associated with long-term suicide. Hopelessness predicted long-term suicides better than short-term suicides, although both suicidal groups had higher mean ratings than the patients who did not commit suicide. It is also notable that two symptoms—diminished concentration and indecisiveness—were marginally significant in predicting both long- and short-term suicides.

DISCUSSION

The variables produced by the first discriminant function analysis, which correctly identified 13 of 14 suicides occurring in the first year following the beginning of the study, did not identify in better than chance fashion the 11 suicides occurring in the 2–10 years after the intake evaluation. This, plus the fact that the variables associated with suicide in the first year did not include the presence of standard predictors such as suicidal ideation and history of previous suicide attempts, led us to look at time from clinical assessment

to suicide as a possible basis for the unexpected variables that emerged (i.e., panic attacks, somatic anxiety, and loss of interest and pleasure [anhedonia]) (7, 12).

The effect of treatment on outcome could not be assessed because eight suicides occurred before the first follow-up visit, when the previous 6 months of treatment was recorded, and because treatment was assigned in a heterogeneous fashion with variable compliance, leaving insufficient numbers of patients in each treatment subgroup (especially among the two suicide groups) for meaningful analysis.

This report suggests two neglected aspects of suicide research that may be of importance for the timely identification of patients suffering from major affective disorders and in danger of suicide: prospective study data and the temporal nature of suicide prediction. The two issues are not really separable because prospective measurement is necessary in order to assess the temporal nature of symptom predictors. In this analysis, the mean symptom levels of traditional suicide predictors (suicidal ideation and previous suicide attempts) among patients who completed suicide within 1 year were well below those of the patients who did not commit suicide, but among patients who committed suicide within 2–10 years they were significantly above those of the patients who did not commit suicide. This finding effectively cancels out any simple direct association between suicide ideation or attempts and completed suicide in the total patient sample. This canceling out effect, based on time to suicide, explains why analyses combining short-term and long-term suicides into one group, such as was done in our previously reported univariate analyses (10), did not find suicidal ideation and suicide attempts to be correlates of completed suicide.

The results of our follow-up study suggest that in this sample of patients with major affective disorders, the three symptoms most strongly related to completed suicide within 1 year of assessment were the anxiety-related symptoms of panic attacks, psychic anxiety, global insomnia, diminished concentration, and alcohol abuse. Loss of interest and pleasure (anhedonia) was also significantly more severe in these patients. Hopelessness, a risk factor that reflects a negative affective evaluation of the world, was found to be associated with completed suicide in the studies of Beck et al. (13). We found, however, that hopelessness was significantly more severe in the patients who completed suicide within 2–10 years than in patients who had not committed suicide only when these groups were compared by using the Mann-Whitney U statistic (see table 2). Risk factors that reflect a patient's current or past preoccupation with suicidal behavior (i.e., suicidal ideation expressed to a clinician and previous history of suicide attempts) are related to completed suicide occurring 1 year or more after assessment.

Inspection of the mean incremental differences in SADS ratings of the discriminating items suggests that some of the differences are clinically as well as statistically significant. That is, the mean differences for rat-

ings of psychic anxiety and loss of interest or pleasure (anhedonia) amounted to a full point or more on the 6-point SADS rating scale and were thus observable by clinicians trained to be precise and reliable with their clinical judgments (14, 15). On the other hand, when viewed from the perspective of time to suicide, hopelessness did not discriminate patients who committed suicide within 2–10 years from patients who had not committed suicide by a sufficient magnitude (0.6 units on a 6-point rating scale) to be considered clinically discriminable. However, the mean difference between patients who had committed suicide within 2–10 years and those who had not was significant (see table 2). Since mean differences of single clinical ratings on SADS items were the basis of measurement, it must be stressed that single clinical dimensions of a specific magnitude are not considered diagnostic of suicide, but a pattern of clinical dimensions (e.g., panic attacks, psychic anxiety, anhedonia, and hopelessness) emerges as an important descriptor of a group of patients at high risk for imminent suicide within weeks up to 1 year after clinical assessment.

Suicidal ideation expressed by a patient with a clinical depression in the course of a clinical assessment is generally accepted as a standard indicator of the presence of suicide risk (12). Yet, in this study most of the patients who completed suicide in the first year after assessment did not communicate the presence of suicidal ideation or plans in response to the specific questions of trained, clinically experienced raters. This finding, somewhat at variance with conventional wisdom, may be related to the prospective design of this study and exactly to whom (clinician or significant other) the patient communicates suicidal ideations. It is possible that instead of communicating suicidal ideation or intent to clinicians, who may try to intervene, patients make tangential communications to relatives, the significance of which is understood in many instances only after the suicide (the previous studies of suicidal communication were all retrospective). This would suggest that the clinician should gather the data for suicide risk assessments not only from the patient but also from significant others (16).

Some of the risk factors correlated with short-term suicide may be modifiable through clinical and therapeutic efforts, thus potentially decreasing the likelihood of suicide. The anxiety-related symptoms in particular may be more rapidly amenable to psychopharmacological or psychotherapeutic interventions than other presuicidal depressive symptoms, such as hopelessness and severe anhedonia. We call symptoms that may be responsive to early clinical intervention "modifiable risk factors."

On the basis of our findings, clinical decision making and research about suicide may benefit from conceptualizing clinical assessments in terms of the differences between acute and long-term and modifiable or nonmodifiable risk factors. This time-related, intervention-oriented focus, which is not emphasized in the current literature on suicide prediction, may help the

clinician to weigh individual clinical observations more appropriately when making suicide risk assessments and may also point in a useful direction for treatment intervention efforts.

In the present analysis, the modifiable risk factors of short-term risk, such as panic attacks, global insomnia, and high levels of psychic anxiety, appear to be the best indicators of acute suicidal risk in combination with moderate alcohol abuse, severe anhedonia, diminished concentration, and indecisiveness. The clinical observation and treatment of severe anxiety symptoms may be one of the leading priorities for treating the acutely suicidal patient with affective disorder. This finding is similar to a position suggested in Shneidman's more theoretical discussion (17).

In a prospective study of completed suicide by psychiatric patients during the 5 years following hospital admission, Pokorny (6) pointed out that psychiatrists deal with a time frame consisting of "minutes, hours, or days" to define and respond to a "suicidal crisis" period, unlike the frame of months or years used by clinical researchers. What is needed is a better definition of the attributes of an acute suicidal crisis in order to provide a basis for more successful intervention. Short-term risk factors in patients with major affective disorders, such as panic attacks, severe psychic anxiety, and alcohol abuse, in the context of severe anhedonia and hopelessness, may help define the acute suicidal crisis and point to therapeutic interventions that may substantially reduce acute suicidal risk. The emergence of panic and anxiety as short-term risk factors may converge with the finding of Coryell et al. (18, 19) of high rates of suicide in patients with panic disorder. More recently, Weissman et al. (20) have shown a relationship between high rates of suicide attempts and panic disorder. Both of these studies add validity to the importance of severe anxiety symptoms as precipitants of suicide.

The findings of different predictors based on time to suicide in this sample suggest that the long-term suicide patients in this study may have had symptoms similar to those of the short-term group within a year of their suicide. Efforts are being made to test this hypothesis on the basis of data concerning relapse and symptom patterns in the year before suicide in the long-term suicide group. The sample of suicides presented in this report is small relative to the universe of patients who commit suicide. Since the findings derive from a sample of Caucasian patients diagnosed as having RDC major affective disorders, it is unknown if these findings would apply in other risk groups, such as non-Caucasian patients or patients with schizophrenia, alcoholism, or personality disorders, raising questions of generalizability of these findings to clinical practice. Although the age range of the patients who committed suicide was 21–73 and half of the patients were 36 or younger, the effects of differences in age are difficult to assess because of the small numbers of suicides across the age spectrum.

Although the outcome of this limited sample sug-

gests that such traditional risk factors as previous history of suicide attempts and suicidal ideation were not highly predictive of short-term suicide, such factors should not be dismissed in the clinical assessment of suicide risk. Rather, these initial findings should draw the attention of clinicians and research investigators to the following issues: 1) the importance of standardized prospective data for studies of completed suicide, 2) the importance of assessing patients in terms of acute versus long-term suicide risk, and 3) the possible value of anxiety symptoms (panic attacks, psychic anxiety, psychomotor agitation, global insomnia) as precursors of suicide and target symptoms for vigorous treatment efforts. Further studies of patients with major depression will be required to replicate these results. Continued follow-up of patients in the sample who have revealed long-term risk factors is currently underway. Our findings replicate those of other investigators in identifying severe hopelessness as a precursor of suicide but add severe anhedonia as a precursor as well.

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Life Events and the Course of Bipolar Disorder

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The authors examined the impact of life stress on the course of bipolar disorder over a 2-year period in a group of 61 outpatients. The patients were followed prospectively with ongoing assessments of stressful life events, symptoms, levels of maintenance medication, and compliance with treatment regimens. As predicted, survival analyses indicated a significant association between life events and relapse or recurrence of the disorder. These effects could not be explained by differences in levels of medication or compliance. Further research is recommended to examine which specific subgroups of bipolar patients are most susceptible to stress.

(Am J Psychiatry 1990; 147:1194–1198)

D espite the consistent finding of modest but significant associations between stress and unipolar depressive symptoms (1–5) and recent theoretical and methodological improvements in research on stress and illness, there have been few rigorous investigations of the impact of stress on the course of bipolar illness. Given that bipolar illness is a recurrent disorder (6), with high rates of considerable exacerbation of symp-

toms over a 1- to 2-year period even when patients apparently comply with lithium carbonate treatment regimens (7), studies examining the factors that predict recurrence and relapse are essential. While genetic and biological components are undoubtedly important in the etiology of bipolar disorder, such factors alone do not entirely explain the variance in the expression of the illness or the timing and frequency of symptoms (8). Psychosocial factors are likely to affect the onset, course, and resolution of this disorder.

Hirschfeld and Cross (9) surveyed the results of controlled and uncontrolled studies of stress and bipolar disorder and concluded that most studies reported that the subjects experienced increased stress before onset or subsequent episodes of the disorder. Results from these studies must be interpreted cautiously, however, given the pervasive methodological flaws and theoretical limitations. First, the use of retrospective designs with lengthy recall periods and questionnaire methods may have contributed to biased or incomplete reporting, errors in memory, inadequate sampling of relevant events, and inaccuracies in dating event onset and duration (5, 10, 11). The only study that used a prospective design to assess stress and symptom levels in 38 patients during a 7-month observation period found few differences in frequency or type of stress between the patients who remained well and those who relapsed (12). However, this investigation may not have used an adequately long observation period and did not control for the effects of medication or compliance with medication regimens, despite the possible effect of these variables on stress-illness relationships.

The present study examined the impact of life stress on the course of bipolar illness over a 2-year period in carefully diagnosed bipolar patients in treatment at an outpatient medication clinic. Prospective methods of assessing symptoms and life stress that have been effective in elucidating the relationships between life stress and unipolar illness were used. In particular, interviews about stressful events and their context, based on methods developed by Brown, Harris, and colleagues (1), were used to obtain careful dating of events and to yield reliable, objective ratings of stressfulness. Symptom levels, diagnoses, and medication and compliance levels were ascertained, independent of the life stress interviews, during the patients' ongoing medication visits to the clinic. The longitudinal design permitted the use of sophisticated techniques such as survival analysis, which incorporates life table and regression analyses, to evaluate the association between probability of relapse and life events. It was hypothesized that patients experiencing increased life stress would have a higher likelihood of relapse as time passed than would patients having lower levels of stress.

METHOD

The participants were outpatients at an affective disorders clinic who were receiving medication for bipolar disorders. Patients were recruited into the ongoing longitudinal study of life stress and course of affective disorder after being followed at the clinic for at least 4 months and after achieving remission status (defined as no episodes of major depression, mania, or hypomania for at least 2 months) or, for a minority of patients, best clinical state (defined as a stable symptom picture for at least the past 6 months).

The subjects were 61 adults (28 men and 33 women) who were followed for at least 1 year. Forty-six were diagnosed as having bipolar I disorder and 15 as having bipolar II disorder. All had experienced prior episodes. Their mean±SD age was 39.6±10.2 years. Eighty-five percent (N=52) of the group was white; 26% (N=16) were currently married or cohabiting, 51% (N=31) were single, and 23% (N=14) were divorced. Forty-one percent (N=25) had at least a college education, and 59% (N=36) had completed high school or less.

Procedures

Initial diagnostic evaluation. Upon admission to the clinic for treatment, each patient received a 3- to 5-hour standard evaluation by a psychiatrist and a psychologist or psychology intern. Detailed information regarding the nature, duration, and dates of current and past symptoms, pharmacologic and psychosocial treatment and treatment response, and family history was obtained from diagnostic interviews (clinical interview, Family History Research Diagnostic Criteria

[13]) and self-report questionnaires. Each patient agreed to be contacted in the future for research purposes. Supplementary information for some patients was provided by interviews with family members and review of past medical records. The kappa coefficient of agreement on *DSM-III-R* axis I diagnoses was 0.80 for a random sample of 39 of the patients.

Ongoing symptom assessment. The ongoing symptom status of the patients was assessed when they attended the medication clinic, at intervals (depending on individual need) of 3 days to 3 months. At each visit the patient's psychiatrist evaluated both current symptoms and symptom status throughout the period since the last medication visit, using the *DSM-III-R* criteria for mania, hypomania, major depression, dysthymia, and mixed states. The duration and dates of any diagnosable episodes and subsyndromal disturbances were carefully noted on clinical research forms, and these data were transferred onto individual symptom time lines that indicated the onset and end of all affective episodes during the observation period.

In addition, psychiatrists used a 4-point scale to rate the patient's current diagnosis, current medication regimen, any medication changes or laboratory results, and compliance with the treatment regimen. The research staff monitored the records closely for completeness and accuracy.

Life stress assessment. Life stress that had occurred during the past 6 months was first assessed with a 45- to 90-minute semistructured face-to-face interview when the patient entered the study. Every 3 months thereafter, all subjects were interviewed by telephone or in person about the occurrence of life events since the last contact.

Life stress interviews were based on the methods of Brown, Harris, and colleagues (1) and were conducted to minimize the patients' reporting biases and forgetfulness, while also evaluating the impact of each event in the context in which the event occurred. The 3-month interval minimized the time period over which the subject had to remember, and the accuracy of life event dating was enhanced by the use of cues to aid the subject's memory. Distortions due to selective recall and symptoms were minimized by the prospective design of the study and by conducting the first interview while the subject was in a state of remission.

The life stress interview included standardized probes to obtain detailed information about the date, duration, nature, and circumstances of each event, including the expectedness, the subjective impact, the desirability, and the resources for coping with the event. Definitions of what constituted an event were based on guidelines from Paykel and Mangen's Interview for Recent Life Events (unpublished manuscript, 1981). Each event was described in a written summary prepared by the interviewer, specifically omitting descriptions of the individual's reactions to the event.

Following procedures described by Brown and Harris (1) and Paykel and Mangen (unpublished manuscript, 1981), after the interview a research team eval-

TABLE 1. Maintenance Treatment Scale Used to Rate Treatment Level of 61 Patients With Bipolar Disorder

Maintenance Treatment Level[a]	Lithium (meq/liter)	Carba-mazepine (mg/day)	Valproate (mg/day)	Neuro-leptics (mg/day)[b]
0	0.00	0	0	0
1	≤0.54	≤499	≤749	≤299
2	0.55–0.69	500–699	750–1249	300–599
3	0.70–0.89	700–999	1250–1999	600–899
4	≥0.90	≥1000	≥2000	≥900

[a]Each level indicates treatment with one kind of drug at the dose shown.
[b]In chlorpromazine equivalents, according to Hollister's conversion table (15).

TABLE 2. Relative Hazard for Relapse at Various Levels of Stress Compared to Baseline Level for 61 Patients With Bipolar Disorder

Stress Level	Coefficient[a]	Standard Error	t $(df=25)^b$	Relative Hazard
2	0.07	0.60	0.12	1.08
3	−0.10	0.63	−0.15	0.91
4	1.51	0.44	3.41[c]	4.53

[a]Comparison with baseline level of stress (level 1).
[b]df equals number of relapse points minus 3, where "relapse points" refers to the number of days on which relapse occurred relative to entry into the study.
[c]$p<0.001$.

uated each event and made an "objective" rating of its threat or severity (defined as the way the average person would be likely to experience the impact of the event under similar conditions) on a scale ranging from 1 (no threat) to 5 (severe threat). The research team, which consisted of at least two persons blind to the subject's symptom status who had been extensively trained in the use of contextual-threat interviewing techniques, also rated each event along several dimensions. Reliability calculations based on a total of 45 events from 16 patients yielded an intraclass correlation coefficient of 0.77 (p≤0.0001) for overall objective ratings of threat by two independent teams of raters.

Medication and compliance assessment. Since the adequacy of a maintenance medication regimen and the patient's compliance with this regimen can easily affect relapse rates, medication regimens and compliance were noted at each outpatient visit. Medication regimens were evaluated by using a 5-point scale modeled after Keller's summary scales for treatment of acute affective disorder (14). Table 1 shows the maintenance treatment scale, which ranges from 0 (no maintenance treatment) to 4 (a high level of treatment) with regard to the four most common forms of maintenance treatment in bipolar disorder. Ratings of combination medication regimens were computed by adding the levels of the components.

At each outpatient visit, the psychiatrist rated his or her impression of the patient's degree of adherence to the prescribed regimen since the last visit on a scale ranging from 1 (complete adherence) to 4 (refused recommended treatment). Mean ratings across visits were determined for each patient for the various time periods of interest. The resulting scores yielded a rough compliance rating suitable for assessing the role of differences in compliance as an alternative to the role of stressful events in explaining changes in symptom status.

Analysis

The symptom time lines of the patients were inspected, and the date of relapse or recurrence was noted. Thirty-two of the 61 patients experienced hypomania or mania (N=21) or a major depressive episode (N=11) according to the *DSM-III-R* criteria. If a sub-

ject experienced multiple episodes, the first was arbitrarily chosen for examination. These episodes represented recurrences in 22 patients (who had been symptom free for at least 1 month before onset of diagnosable disorder) and relapses in 10 (who went into an episode representing exacerbation of mild previous symptoms). For these 32 patients, the total of objective ratings of stress for events occurring in the 3 months before symptom change was calculated. Of the remaining subjects, 21 experienced no episode, and seven dropped out of the study before completing the first year. Of the no-episode patients, 11 were symptom free over the entire period, and 10 experienced minor, nondiagnosable symptoms. For this group, the final 3 months of the observation period were used to compute totals of objective ratings of life event stress.

We used survival analysis to evaluate the association between stress and symptoms in terms of the probability of symptom change given the stress level, measured by time to episode onset. A variation of Cox's proportional hazards model (16), incorporating stress as a time-dependent covariate, was used. Following the method of Gail (17), we divided the total objective ratings of stress before relapse into quartiles and then calculated coefficients comparing the hazard for the baseline level of stress to the hazard for higher levels.

RESULTS

There was a significant relationship between the highest levels of stress and the likelihood of relapse (see table 2). As table 2 indicates, the patients with low and average levels of stress did not have a greater risk of relapse than those without stress, but those with the highest levels had a risk 4.53 times higher than the patients without stress.

To rule out the confounding effects of differences in the intensity of medication treatment or the level of compliance with regimens, patients who did experience new affective episodes were compared to patients who did not. When the mean medication ratings shown in table 1 for the 3-month comparison periods were used, a t test indicated no significant difference in treatment between those who had an episode and those who did not (t=1.16, df=45, p=0.25, two-tailed

test). Similarly, mean compliance ratings for the comparable periods did not differ for the two symptom group (t<1, df=38, p=0.40). Thus, level of medication and compliance with medication regimens did not explain the differential relapse/recurrence rates of the two groups.

DISCUSSION

The longitudinal analysis of symptom changes in bipolar patients indicated a significantly greater likelihood of relapse in the patients with high stress levels than in the patients with lower stress levels and the patients who did not relapse. The subjects who had no stress or low or average levels of stress did not show a greater risk of relapse than those who stayed well. The following representative case example highlights the importance of this finding.

Case 1. Mr. A, a 30-year-old man, had been given a diagnosis of bipolar I disorder at age 21. He had had two manic episodes and multiple minor depressions and hypomanic episodes before treatment at the affective disorders clinic. After entering the study, he remained asymptomatic on a regimen of lithium carbonate and had no severely threatening life events (those rated 4 or 5 on the objective threat scale) during the first 6 months of observation. Then the patient reported a severely threatening event that involved a month-long financial investigation at his workplace. Directly afterward he experienced a mild subsyndromal depression, which spontaneously resolved after 18 days. Several weeks later, however, Mr. A reported three severely threatening events over the course of a month, two of which were employment-related changes that jeopardized his job, and one of which involved a major estrangement from his live-in girlfriend. One week after these events, he had a 2-week manic episode, which was controlled on an outpatient basis with an increased dose of lithium and which subsided into hypomania that persisted for over 3 months.

In this patient's case, each severe event occurred during an asymptomatic period, and several were closely associated with his subsequent manic relapse. He also reported milder stressful events throughout the observation period, which may have added to his risk of relapse.

The results of this study are consistent with those of studies based on retrospective event reporting that have indicated an association in some bipolar patients between stressors and episodes of illness. However, this study is the first to demonstrate this association between symptoms and stress by using a prospective design, systematic interview procedures, and survival analysis. Although the sample size was limited, the results are particularly suggestive because of the longitudinal design of the study. The results have both theoretical and clinical implications.

Theoretically, the results affirm the impact of psychosocial factors on the course of an affective disorder with a presumed biological base. At present there is no complete model for integrating psychological and bio-

logical factors in the course of bipolar disorder. One promising approach, however, is that of Goplerud and Depue (18), who argued that some forms of bipolar disorder may involve weak inhibitory modulation in certain CNS systems which control behavioral and biological variables and that stress contributes to dysregulation of such variables. A different model has been proposed by Wehr et al. (19), who suggested that sleep reduction, often a concomitant of stressful life circumstances, may be a final common pathway precipitating mania. Clearly, future efforts to integrate biological and psychosocial factors will improve the prediction of the course of bipolar disorder.

Clinically, an important implication of our findings is the possibility that reducing the impact of stressful life events on patients' lives may help to prevent episodes of affective disorder. Both psychological and medical interventions might need to be increased at times of stress, and it might be important for clinicians to carefully monitor the occurrence of stressors in patients' lives and to be alert to the effects of the events over a period of several months.

It is noteworthy that the results could not be explained by differences in the adequacy of medication regimens or by differences in the level of compliance with these regimens. There were no significant differences between the group that relapsed and the group that did not in maintenance medication levels or in medication compliance ratings, which could account for changes in symptoms and thus provide an alternative explanation to the effects of stress. Nevertheless, in some individuals it is likely that the effects of stressful events may indeed be mediated by changes in compliance with medication regimens. In individual cases, stressors may have a complex interaction with symptoms and compliance behavior, sometimes leading to the exacerbation of symptoms because of the patient's failure to adhere to the medication regimen.

It is also important to note that relapse was more likely only in patients who experienced high levels of stress over the observation period. It appears that there may be a threshold at which a patient becomes more vulnerable to the impact of threatening events. Individuals with lower levels of stress did not differ in risk of relapse from individuals who remained episode free. This finding is consistent with research on associations between life stress and unipolar disorder, suggesting that episodes and symptoms are associated with severely threatening events or chronic strain (1, 5).

Although there was a significant overall effect linking changes in symptoms and high degrees of stress, a larger sample size is necessary to replicate the results of this pilot study. Further, the demonstrated relationship between stress and relapse is not invariable for all bipolar patients. There appeared to be some subjects who experienced major stressors but did not have an increase in symptoms, while some individuals had an increase in symptoms apparently in the absence of major life events. In a previous study (20), we showed that, at least for unipolar patients, the personal mean-

ing of events, rather than simply the occurrence of the events, is associated with depression. In addition to the personal meaning of events, there are a number of factors, such as psychiatric history and family history of affective disorders, that might affect reactions to stress in bipolar patients. Further exploration of these issues is underway and promises to help clarify the impact of stressful life events on the individual course of disorder and to aid in the construction of models that predict the course of bipolar illness from various combinations of psychosocial, genetic, and psychiatric factors.

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Comorbidity of Major Depression and Anxiety Disorders in Twin Pairs

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The relationship among major depression only, major depression with anxiety disorders, and anxiety disorders only was investigated in a twin sample (N=177 pairs). The results suggest that there is an etiological relationship between mixed major depression-anxiety disorders and major depression only but no relationship between these two conditions and anxiety disorders only. When anxiety disorders with panic attacks were analyzed, the relationship between mixed cases and major depression only and the lack of a relationship between mixed cases, major depression only, and anxiety disorders only became even clearer. Furthermore, mixed cases seemed to be more strongly influenced by genetic factors than was major depression only.
(Am J Psychiatry 1990; 147:1199–1202)

T he question about the unitarian or dual etiology of anxiety and depression has long been the subject of debate in British and, to a lesser extent, American psychiatry (1). The debate has often been mixed with the question about the distinction between psychoses and neuroses and between endogenous and reactive affective states. The American classification system for mental disorders, *DSM-III*, aimed to solve the debate by abolishing the distinction between psychotic and nonpsychotic unipolar affective disorders, while at the same time sharply distinguishing anxiety disorders from affective disorders. Major depression was placed above anxiety disorders in the diagnostic hierarchy, which means that when a patient has both anxiety disorders and major depression, the latter should be the sole diagnosis. It soon became clear that the hierarchy had to be applied often (2). The presence of major depression strongly increased the likelihood of the presence of an anxiety disorder.

Family studies of anxiety disorders have supported a distinction between major depression and anxiety disorders, as relatives of probands with anxiety disorders

have not been found to have a higher frequency of major depression than do relatives of control subjects (3, 4). The Yale family studies (5–7), on the other hand, disclosed that first-degree relatives of individuals with both major depression and anxiety disorder had a higher frequency of major depression, as well as anxiety disorders, than did relatives of individuals with major depression only. However, it seems as if a higher frequency of depression is seen among relatives of probands with concurrent depression and anxiety disorder, not among relatives of probands with depression secondary to an anxiety disorder (8, 9). The results of the family studies seem therefore equivocal in regard to a common etiology of anxiety disorder and depression.

Twin studies might better disclose a common genetic diathesis for anxiety disorders and depression. An Australian twin study from the general population (10) seems to have shown that anxiety disorders and depression have a common genetic basis, while environmental factors create the differentiation. However, the conclusions from the study have been disputed (11). And, in any case, the study did not deal with clinical cases.

The present study, a reanalysis of the Norwegian twin study (12, 13), aimed at the disclosure of any etiological relationship between major depression and anxiety disorders.

METHOD

The methodology of the Norwegian twin study has been described earlier (12, 13). Same-sexed twins were identified by comparing with a national twin register all patients who were treated in Norway for neurotic or borderline conditions before 1977 and were born between 1910 and 1955. All twins were personally interviewed. The Present State Examination (PSE) (14) was used, with the modification that lifetime symptoms were recorded. Information was also obtained from psychiatric records. *DSM-III* diagnoses were obtained by means of a computer output of the PSE symptoms and, if necessary, a case summary of the interview. The hierarchy of *DSM-III* was not used in the present analysis. A probandwise method was applied; that is, both twins in a twin pair were index

TABLE 1. Concordance of Diagnoses of Co-Twins and Probands With Major Depression Without and With Anxiety Disorders and Anxiety Disorders Without Major Depression

Proband Diagnosis	Total N	Co-Twin Diagnosis						
		Major Depression Only		Major Depression With Anxiety		Anxiety Disorder Only	
		N	%	N	%	N	%
Major depression only							
Monozygotic	16	1	6.3	3	18.8	0	0.0
Dizygotic	25	2	8.0	2	8.0	2	8.0
Major depression with anxiety							
Monozygotic	17	5[a]	29.4	1	5.9	2	11.8
Dizygotic	34	4[a]	11.8	0	0.0	4	11.8
Anxiety disorder only							
Monozygotic	32	1	3.1	0	0.0	11	34.4
Dizygotic	53	2	3.8	0	0.0	9	17.0

[a]One co-twin had a bipolar disorder.

twins if they were independently identified by the ascertainment process.

The study population consisted of 177 twin pairs. Forty-one of the index twins had major depression without anxiety disorders, 51 had major depression with a lifetime diagnosis of anxiety disorder, and 31 had both major depression and anxiety disorder with panic attacks. Eighty-five index twins had an anxiety disorder without major depression, and 41 had an anxiety disorder with panic attacks without any episode of major depression. Because they were lifetime diagnoses, anxiety and depression appeared in different order, concurrent and subsequent. Any effort to have separated the index twins according to course might have drastically reduced the number of twins.

The mean age at interview was similar in all groups of index twins: 48 years (range, 24–66) for twins with major depression only, 45 years (range, 21–66) for the group with major depression and anxiety disorder, and 44 years (range, 22–66) for the group with anxiety disorder only. The proportion of women was as follows: major depression only, 78% (N=32); mixed anxiety disorder and major depression, 84% (N=43); and anxiety disorder only, 66% (N=56). When only anxiety disorders with panic attacks were considered, the mean ages were as follows: 47 years (range, 24–66) for the major depression index twin group, 45 years (range, 21–66) for the mixed group, and 45 years (range, 22–66) for the group with anxiety disorder with panic attacks. Seventy-five percent (N=46) of the index twins with major depression only were women, as much as 94% (N=27) of the index twins with major depression and anxiety disorders with panic attacks were women, and only 56% (N=23) of the index twins with anxiety disorder with panic attacks only were women.

The probandwise concordance between probands and co-twins was displayed through the calculation of odds ratio, which is a measurement of association between two bivariate variables. The statistical significance of the relationship was calculated by means of stepwise logistic analysis, which included age at interview and sex; the analysis used the LOGIST procedure in the Statistical Analysis System (15).

RESULTS

Table 1 shows that pure anxiety disorders were uncommon among co-twins of probands with pure major depression, and, correspondingly, pure major depression was infrequent among co-twins of probands with pure anxiety disorders. Mixed anxiety disorder and depression was, however, common among co-twins of probands with pure major depression, and pure major depression was common among co-twins of probands with mixed anxiety and depression.

The concordance of pure depression and mixed anxiety-depression was almost three times as high in monozygotic pairs as in dizygotic pairs. In the calculation of odds ratios between diagnoses in probands and co-twins, a stepwise logistic regression was performed, with co-twins' diagnoses as dependent variables and probands' sex, diagnoses, and age at interview as independent variables. The analysis showed that for monozygotic twins, there was a statistically significant relationship between major depression without anxiety in probands and major depression with anxiety in co-twins (odds ratio=11.1, ±95% confidence interval=1.1–115.5; p<0.05 when age and sex were taken into consideration). A corresponding statistically significant relationship existed between major depression with anxiety in monozygotic probands and major depression without anxiety in co-twins (odds ratio= 9.6, 95% confidence interval=1.7–55.6; p<0.02 when age and sex were taken into consideration). Finally, there was a statistically significant relationship between anxiety disorders without major depression in monozygotic probands and co-twins with the same diagnosis (odds ratio=8.1, 95% confidence interval= 1.6–40.4; p<0.02 when age and sex were taken into consideration).

No relationship between diagnoses in dizygotic probands and co-twins was statistically significant. Appli-

TABLE 2. Concordance of Diagnoses of Co-Twins and Probands With Major Depression Without and With Panic Attacks and Anxiety Disorders With Panic Attacks Without Major Depression

| Proband Diagnosis | Total N | Co-Twin Diagnosis | | | | | |
| | | Major Depression Only | | Major Depression With Panic Attacks | | Anxiety Disorder With Panic Attacks Only[a] | |
		N	%	N	%	N	%
Major depression only							
Monozygotic	24	2	8.3	3	12.5	2	8.3
Dizygotic	37	2	5.4	2	5.4	2	5.4
Major depression with panic attacks							
Monozygotic	9	5[b]	55.5	0	0.0	0	0.0
Dizygotic	22	4[b]	18.2	0	0.0	1	4.5
Anxiety disorder with panic attacks only							
Monozygotic	18	0	0.0	0	0.0	4	22.2
Dizygotic	23	0	0.0	0	0.0	0	0.0

[a]Consists of panic disorder, agoraphobia with panic attacks, and generalized anxiety disorder with panic attacks.
[b]One co-twin had a bipolar disorder.

cation of logistic regression with zygosity as the independent variable showed no statistically significant effect of zygosity. This result leads us to the suggestion that there is an etiological relationship between pure major depression and mixed anxiety-depression but no relationship between these two groups of disorders and pure anxiety disorders. As the relationship was only statistically significant for monozygotic twins, the possibility exists that the relationship is genetic, even though zygosity did not yield a significant effect in the logistic regression.

As the debate most often has revolved around the question of whether there is an association between panic disorders and major depression, table 2 has restricted the anxiety disorders to cases with panic attacks. The anxiety disorders with panic attacks in table 2 consist of panic disorder, agoraphobia with panic attacks, and generalized anxiety disorder with panic attacks. The three groups of anxiety disorders are classified together to make the number of twin pairs larger, because a genetic linkage study has suggested that the three disorders have the same etiology (16) and because the same pattern was disclosed for all three groups of anxiety disorders.

Table 2, even more dramatically than table 1, discloses a lack of familial or genetic relationship between pure anxiety disorders with panic attacks and major depression with and without anxiety disorders with panic. The odds ratios for major depression with panic attacks in probands and major depression without panic attacks in co-twins were statistically significant when age and sex were taken into consideration in the stepwise logistic regression. The relationship was significant for dizygotic twins (odds ratio=6.4, 95% confidence interval=1.1–38.1; p<0.002) as well as for monozygotic twins (odds ratio=25.0, 95% confidence interval=3.6–173.2; p<0.05). Furthermore, when zygosity was an independent variable, this variable also had a significant effect on the results (p<0.05). On the basis of our findings, it thus seems as if major depres-

sion with panic attacks is etiologically and probably also genetically related to major depression without panic attacks. Panic attacks without major depression seem unrelated to major depression with and without anxiety. As earlier studies noted (12, 13), age at onset did not influence the concordance rates.

DISCUSSION

The present study started before the era of *DSM-III*. Hence, the diagnostic interview applied, PSE, is not based on *DSM-III*. Even so, PSE is so detailed according to symptoms and clinical features that it seems possible to derive *DSM-III* diagnoses based on the interview. However, some uncertainty might be attached to the results when an interview schedule not closely corresponding to *DSM-III* is applied.

The diagnoses were not obtained blindly from judges, and reliability estimates were not calculated. Instead, application of algorithms to the computerized symptoms helped make the assessment blindly. Whether this precaution might reduce the validity of the diagnoses is difficult to know. Furthermore, the limitation of twin studies will always be the number of twin pairs. Hence, the possibility always exists that the results are due to pure chance. The statistical tests might help to avoid this misinterpretation. However, the astonishing fact that co-twins of index twins with major depression alone so seldom had only major depression, but rather had mixed anxiety-depression and vice versa, might be due to the low number of twin pairs. The difference between concordance rates among monozygotic and dizygotic twins might also be due to chance. Furthermore, a higher concordance among monozygotic than dizygotic twins might be a consequence of a more similar environment for monozygotic twin partners than for dizygotic twin partners.

That a relationship between major depression only and mixed depression-anxiety was not evident in cases

where major depression only was the proband diagnosis might be because probands with major depression only had a lower liability for depression than did mixed cases. In accordance with a multiple threshold theory, one could interpret the results as showing that mixed cases had a higher liability for depression because of a number of genetic and environmental factors (17).

In any case, the present analysis of twin data might indicate that there is no etiological connection between stable anxiety only or anxiety with panic attacks only and major depression. Conditions characterized by concurrent or subsequent episodes of anxiety disorders and major depression, on the other hand, seem to be genetically or environmentally related to major depression without anxiety. Furthermore, anxiety or panic attacks might be an indication of a stronger genetic determination of the mood disorder.

The results of the present study are in accordance with earlier family studies showing no depression among relatives of probands with panic attacks only (8). Several studies have not used a group with anxiety only but have distinguished between primary anxiety and secondary depression, on the one hand, and concurrent anxiety and depression, on the other hand. The primary anxiety group might be assumed to be closest to the anxiety only group. Two of these studies (8, 9) have shown a lower frequency of depression and a higher frequency of anxiety among the relatives of probands with primary anxiety. Another study (5, 6) did not report any difference. However, all three studies, as well as the study of Weissman et al. (7), show that probands with both anxiety and depression have more relatives with depression than do probands with depression only. The Australian twin study (10) may also be interpreted as suggesting not only a common genetic diathesis for anxiety and depressive symptoms (10), but also a specific genetic influence on panic anxiety, according to the most recent publication from the research team (18).

The viewpoint that mixed depression and anxiety disorders might be more strongly influenced by genetic factors than is pure depression might explain why subjects with the mixed disorders have more severe symptoms and poorer prognosis (8, 9) and more often have severe concomitant personality disorders (17–20). Hence, even if the mixed cases etiologically may be within the major depression spectrum, they deserve special attention as a more severe variant of the mood disorders.

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Amoxapine Versus Amitriptyline Combined With Perphenazine in the Treatment of Psychotic Depression

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In a double-blind study lasting for 4 weeks, the authors compared the effectiveness of amoxapine, an antidepressant with potential antipsychotic properties, with a combination of amitriptyline plus perphenazine in the treatment of 38 patients who had the diagnosis of major depression with psychotic features (psychotic or delusional depression). Patients in each group showed similar improvement in depression and psychosis. There was a tendency for the patients treated with amitriptyline plus perphenazine to have higher global response rates. However, the patients given amoxapine had significantly fewer extrapyramidal side effects.
(Am J Psychiatry 1990; 147:1203–1208)

M ajor depression with psychotic features, which is often referred to as psychotic depression or delusional depression, is thought to represent an illness with clinical features distinct from those of nonpsychotic major depression (1–4). There is evidence suggesting that there are also biological differences between psychotic and nonpsychotic depression (5–14). Most important for patient care, however, is the difference between psychotic and nonpsychotic depression in pharmacological response.

A review of the literature (15), which consisted mainly of retrospective and uncontrolled prospective studies of 1,054 patients, found that although 67% of patients with nonpsychotic depression responded to tricyclic antidepressants, only 35% of psychotically depressed patients responded to these drugs when used alone. In contrast, several retrospective and open prospective studies have suggested a much better response rate (60%–80%) to the combination of a tricyclic antidepressant and an antipsychotic medication (1, 3, 16–19). Most importantly, in the first randomized double-blind pharmacological prospective study in delusional depression, Spiker et al. (20) compared the tricyclic amitriptyline with the antipsychotic perphenazine and then compared both of these with the combination of amitriptyline and perphenazine. Their results confirmed the data from the retrospective studies in that 47% of their patients responded to amitriptyline alone, 19% to perphenazine alone, and 78% to the combination of both drugs. When the results of the many retrospective studies and this well-designed prospective study are taken together, it appears clear that the combination of an antidepressant and an antipsychotic is the pharmacological treatment of choice in this disorder. The efficacy of this combination in the treatment of psychotic depression has been attributed to blockade of an overactive dopamine system and augmentation of a deficient norepinephrine, or perhaps serotonin (5-HT), system in the CNS of psychotically depressed patients (1).

The antidepressant drug amoxapine, the N-desmethyl derivative of the antipsychotic drug loxapine, and its 7-OH metabolite appear to possess effects similar to those of other neuroleptic drugs in vitro (21–23) and in vivo (22, 24, 25). In addition, amoxapine's biochemical (21, 26) and clinical (27, 28) profiles are similar to those of other tricyclic antidepressants. These combinations of pharmacological qualities make amoxapine worthy of study in the treatment of psychotic depression.

We have previously described the usefulness of amoxapine in the management of psychotically depressed hospitalized patients (29–31). In these open trials 60%–80% of patients had a clinically significant response to treatment.

The purpose of the present study was to examine more carefully the utility of amoxapine in the treatment of psychotic depression. Amoxapine was compared with a combination of amitriptyline plus perphenazine in a prospective randomized double-blind study in the treatment of hospitalized patients who had the diagnosis of major depression with psychotic features.

METHOD

Subjects for this study were recruited from the inpatient units at two distinct sites. All patients had been admitted for the clinical treatment of their condition and were asked to participate in the study after initial screening, which included judgments of diagnostic suitability and good physical health. Routine physical examination, ECG, and laboratory studies were done to assure that the patients had no substantial physical abnormality, including cardiovascular, neurological, and endocrinological problems, that would preclude their receiving study medications. All of the women considered for the study had had a negative urine pregnancy test.

Usually within 1 week of admission, after initial physical and psychiatric screening, patients were interviewed by the research psychiatrist (R.F.A. Jr. or E.A.B. Jr.). Treating psychiatrists, nurses, and family members also provided information. If the patient met *DSM-III* criteria for major depression with psychotic features and was able to provide informed consent, he or she was invited to participate in the study.

On day 1 of the study the patient was rated for depression by using the 17-item Hamilton Rating Scale for Depression and the Brief Psychiatric Rating Scale (BPRS) as well as the 5-item Clinical Global Evaluation Scale (1=not ill, 5=very severely ill). All patients were given a placebo looking just like the subsequent study drug four times daily. The patients received no other psychiatric medication during this period except for low-dose lorazepam or oxazepam to control extreme agitation or severe insomnia. On day 5 of placebo treatment, the patients were reassessed diagnostically. They were evaluated with the Hamilton depression scale, the BPRS, the Clinical Global Evaluation Scale, and the 5-point Clinical Global Improvement Scale (1=marked improvement, 5=worse). They again had to meet *DSM-III* criteria for major depression with psychotic features. If substantial depression (score greater than 18 on the Hamilton depression scale) and persistent delusions and/or hallucinations were still present, the patients were randomly assigned in a double-blind fashion to treatment with either amoxapine or a combination of amitriptyline plus perphenazine.

Fifty-six patients provided informed consent and entered the placebo washout phase of the study. Ten of these patients were dropped from the study before receiving active medication; four of these patients refused further participation and six improved substantially in their symptoms.

The remaining 46 patients were assigned blindly to either amoxapine (21 patients) or amitriptyline plus perphenazine (25 patients). The patients received identical capsules containing either 100 mg of amoxapine or 50 mg of amitriptyline plus 8 mg of perphenazine. On day 1 and day 2, patients received one capsule of active medication at 9:00 a.m. and 9:00 p.m. and one identical placebo capsule at 1:00 p.m. and 6:00 p.m. On day 3 the patients received active medication cap-

sules at 9:00 a.m., 6:00 p.m., and 9:00 p.m. and a placebo at 1:00 p.m. On day 4 and thereafter, each patient received a capsule of active medication four times daily, for a total daily dose of 400 mg of amoxapine or 200 mg of amitriptyline plus 32 mg of perphenazine. The protocol allowed for a dose reduction of one capsule at any time and an increase of one capsule after 22 days on active medication.

At the end of each treatment week over the 4-week active medication trial, the patients were assessed for global improvement (by using the Clinical Global Improvement Scale and the Clinical Global Evaluation Scale) and side effects by the research psychiatrists and rated for depression and psychosis by a trained research assistant using the Hamilton depression scale and the BPRS. These scales and scores were reviewed for consistency and validity by the research psychiatrists. Global evaluation took into account reports on the patient's symptoms provided by nurses, treating psychiatrists, and family members. A side effect checklist that included specific extrapyramidal and dyskinetic symptoms was filled out for each patient weekly.

Before the initiation of the study protocol we decided to use as the basis of efficacy analysis only those patients who completed at least 2 weeks of active medication. A one-way analysis of variance was used to compare the two treatment groups on baseline severity measures (Hamilton depression scale, BPRS, Clinical Global Evaluation Scale) and demographic variables such as age. An analysis of covariance (ANCOVA) with the baseline measurement as the covariate was used to analyze the differences in outcome measures (Hamilton depression scale, BPRS, Clinical Global Improvement Scale, and Clinical Global Evaluation Scale) between the two treatment groups at each evaluation period. The thinking disorder subscale of the BPRS (conceptual disorganization, grandiosity, suspiciousness, hallucinations, unusual thought content) was also analyzed in this manner. In addition, a separate ANCOVA was used to evaluate any differences in the outcome measures at the end of the study irrespective of whether the patient completed all 4 weeks of the active medication study protocol.

Categorical data, such as demographic characteristics and illness-related symptoms, as well as categorical outcome measures were analyzed by chi-square analysis.

RESULTS

Of the 46 patients who entered the active medication phase of the study, eight were dropped from the study before receiving 2 full weeks of active medication. Four of the patients receiving amoxapine were dropped from the study early, one for inadequate response and three for refusal to participate. Four patients treated with amitriptyline plus perphenazine were dropped early, one for inadequate response, two for adverse experiences (orthostatic hypotension and constipation), and one for refusal to participate. Since

TABLE 1. Characteristics of the Depressive Illness of 38 Psychotically Depressed Patients Given Amoxapine or Amitriptyline Plus Perphenazine

	Amoxapine (N=17)		Amitriptyline Plus Perphenazine (N=21)	
Characteristic	N	%	N	%
Unipolar	14	82	18	86
Bipolar	3	18	3	14
Melancholic	12	71	11	52
Mood congruent	11	65	10	48
Mood incongruent	6	35	11	52
Delusional	16	94	20	95
With hallucinations	5	29	10	48
With hallucinations only	1	6	1	5

FIGURE 1. Hamilton Depression Scale and BPRS Ratings of 38 Psychotically Depressed Patients Given Amoxapine or Amitriptyline Plus Perphenazine

dropouts from both groups were similar, the plan to analyze the efficacy data for only those patients receiving at least 2 weeks of active medication appeared justified.

There were 38 patients who met this criterion: 17 (mean±SD age=44.4±12.4 years) in the amoxapine group and 21 (mean age=46.1±11.5) in the amitriptyline-perphenazine group. There were 16 men (94% of the total) in the amoxapine group and 16 men (76% of the total) in the amitriptyline-perphenazine group. The racial mix of the groups was similar; in the amoxapine group 12 (71%) of the patients were Caucasian and five (29%) black, and in the amitriptyline-perphenazine group 12 (57%) were Caucasian and nine (43%) were black. For 24 (63%) of the 38 patients, the present affective episode had lasted longer than 3 months; 29 (76%) of the patients had been hospitalized previously for a psychiatric illness; and the 38 patients had had a mean±SD of 4.6±1.6 previous affective episodes. There were no significant differences between the two treatment groups on any of these measures.

The characteristics of the depressive illness of the 38 patients are shown in table 1. Most of the patients in each group had unipolar or melancholic depression. All of the patients manifested delusional thinking except for one patient in each group who had hallucinations as the only psychotic symptom. The distribution of patients with mood-congruent and mood-incongruent psychotic features was similar in both groups (χ^2=0.53, df=1, n.s.).

Nine patients in each group had received either antidepressants or antipsychotic medication in the month before the study. In the amoxapine group, five of the nine patients who had received such medication were considered nonresponders. In the amitriptyline-perphenazine group, six of the nine patients were considered nonresponders.

Eleven of the 17 patients in the amoxapine group received 400 mg of the drug until the end of the study, four received dose increases to 500 mg, and two received dose decreases to 300 mg (both secondary to
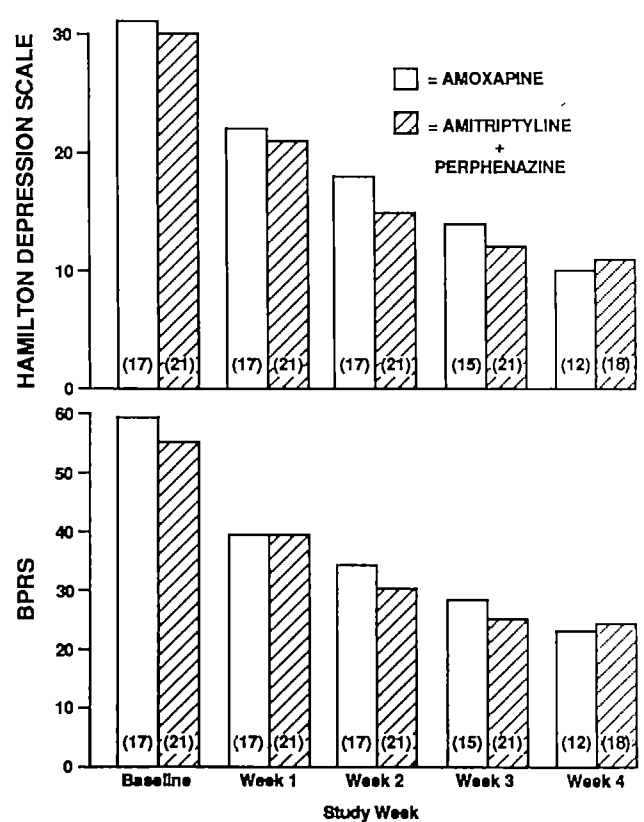
hypotension or dizziness). Eleven of the 21 patients given amitriptyline plus perphenazine received 200 mg of amitriptyline and 32 mg of perphenazine, seven received dose increases to 250 mg of amitriptyline and 40 mg of perphenazine, and three received dose decreases to 150 mg of amitriptyline and 24 mg of perphenazine (all secondary to hypotension or dizziness).

The Hamilton depression scale and BPRS ratings for both patient groups at baseline and over the 4-week active treatment period are given in figure 1. As can be seen the mean ratings on the Hamilton depression scale and the BPRS were similar for both treatment groups at baseline and at each treatment week. ANCOVA showed that there was a significant improvement in both depression and BPRS scores at each treatment week over baseline for both groups. However, there was no significant difference between the two treatment groups at any week.

Since five patients in the amoxapine group and three in the amitriptyline-perphenazine group dropped out before the final ratings were made at week 4, the data were analyzed for between-group differences in the clinical ratings at baseline versus the final ratings, irrespective of when the final rating occurred between week 2 and week 4. These data are summarized in table 2. There was no significant difference between the groups at baseline for measurements of depression,

TABLE 2. Baseline and Final Clinical Ratings of 38 Psychotically Depressed Patients Given Amoxapine or Amitriptyline Plus Perphenazine

Scale	Amoxapine (N=17)		Amitriptyline Plus Perphenazine (N=21)		Comparison	
	Mean	SD	Mean	SD	F^a	p
Hamilton Rating Scale for Depression						
Baseline	31.1	5.6	29.5	5.6	0.70	0.40
Final[b]	11.3	8.9	10.4	8.9	0.11	0.74
BPRS						
Total						
Baseline	59.0	11.4	55.1	11.4	1.08	0.31
Final[b]	35.3	12.9	33.0	12.9	0.29	0.59
Thought disorder subscale						
Baseline	3.0	1.0	3.0	1.0	0.00	0.99
Final[b]	1.9	0.8	2.0	0.8	0.14	0.72
Clinical global evaluation						
Baseline	4.4	0.6	4.3	0.6	0.02	0.88
Final[b]	2.7	1.1	2.1	1.2	2.62	0.11

[a]Calculated by analysis of variance for baseline differences between groups (all df=1, 36) and by analysis of covariance for final rating differences between groups with the baseline values as covariates (all df=1, 35).
[b]The final rating was obtained when the patient ended pharmacotherapy. All patients received medication for at least 2 weeks and for no more than 4 weeks.

TABLE 3. Clinical Effectiveness of Amoxapine or Amitriptyline Plus Perphenazine for 38 Psychotically Depressed Patients

Clinical Measure	Amoxapine (N=17)		Amitriptyline Plus Perphenazine (N=21)		Chi-Square Analysis	
	N	%	N	%	χ^2 (df=1)	p
Change in Hamilton depression score >50%	12	71	17	81	1.27	0.26
Change in BPRS score >50%	10	59	16	76	2.24	0.13
Clinical global improvement						
Marked	8	47	13	62	1.55	0.21
Moderate or marked	14	82	18	86	0.53	0.47
Clinical global evaluation of slight or no illness	10	59	15	71	1.34	0.25

psychosis, or global severity of illness. At the end of the study both groups showed a decrease in depression, psychosis, and severity of illness. However, there was no significant difference between the groups on any of these measures.

To examine how many patients were effectively treated in each medication group, we analyzed global improvement using accepted categorical criteria of improvement. These data are presented in table 3. Although there was a tendency for the patients in the amitriptyline-perphenazine treatment group to do better according to each response criterion, there was no significant difference between the groups on any measure of improvement. Notably, 14 (82%) of the 17 patients given amoxapine and 18 (86%) of the 21 patients given amitriptyline plus perphenazine showed moderate to marked improvement during treatment. For the unipolar patients alone (14 in the amoxapine group and 18 in the amitriptyline-perphenazine group), there was a trend for more of the patients in the amitriptyline-perphenazine group to exhibit a greater than 50% reduction in the Hamilton depression scale and BPRS scores (χ^2=2.9, df=1, p<0.10). However, this trend was not evident in clinical global improvement ratings, where overall re-

sponse rates were high for both groups. Specifically, 12 (86%) of the 14 unipolar patients in the amoxapine group and 17 (94%) of the 18 unipolar patients in the amitriptyline-perphenazine group showed at least moderate improvement.

Side effects experienced by the study participants were similar in each group; anticholinergic effects predominated. These side effects were blurred vision (seven patients in the amoxapine group and 10 in the amitriptyline-perphenazine group), constipation (10 and 16 patients, respectively), and delayed urine flow (four and seven, respectively). Although there was a tendency for more patients in the amitriptyline-perphenazine group to experience anticholinergic side effects, the only side effect to reach statistical significance at the p≤0.05 level was dry mouth, which was experienced by seven (41%) of the patients in the amoxapine group and 15 (71%) of the patients in the amitriptyline-perphenazine group (χ^2=4.88, df=1, p<0.03).

Orthostatic hypotension and dizziness occurred in approximately one-fourth of the patients; there was no significant difference between groups. Altogether, six (13%) of the 46 patients who started the study—two in the amoxapine group and four in the amitriptyline-

perphenazine group—could not tolerate full doses of the medications because of orthostatic hypotension and dizziness.

Extrapyramidal side effects were systematically evaluated and rated. Significantly more patients in the amitriptyline-perphenazine group experienced new or increased tremors or rigidity; two patients in the amoxapine group and nine in the amitriptyline-perphenazine group experienced clinically significant extrapyramidal symptoms ($\chi^2=6.1$, df=1, p<0.02). Most of these symptoms were rated as mild to moderate.

DISCUSSION

The main finding of this study is that amoxapine when given alone can be as efficacious in the treatment of psychotic depression as an accepted standard combination of antidepressant and antipsychotic medications. Specific ratings for both depression and psychosis improved equally in patients given each drug regimen over the 4-week study period. These findings, however, are limited by the sample size, which allows examination of only large differences in treatment effects. Smaller effects can be determined only from larger sample sizes.

There is no evidence from the data presented here that either drug regimen works faster. There was also no significant difference between the treatment groups in global outcome measures such as improvement and level of illness. Although there was an overall tendency for a few more patients in the amitriptyline-perphenazine group to have better global outcomes, whether this is clinically meaningful is not certain. In any case, our data support previous open-label studies suggesting good response rates with amoxapine treatment of psychotic depression (29–31).

In the only major prospective study that, to our knowledge, specifically examined the pharmacological treatment of psychotic (delusional) depression, Spiker et al. (20) clearly found that the amitriptyline-perphenazine combination was superior to each drug used alone. Approximately 70%–80% of the patients treated in both their study and our present study showed a very substantial response to this treatment. With amoxapine treatment, on the other hand, 50%–70% of the patients had similarly excellent outcomes. Although a direct comparison between our study and that of Spiker et al. is tenuous at best, it appears that amoxapine treatment resulted in somewhat better response rates than did amitriptyline alone.

When a pharmacological regimen is chosen to treat an illness such as psychotic depression, other variables, such as patient acceptance, compliance, and side effects (both acute and chronic), must be considered. Generally, both treatment regimens caused similar side effects, except for extrapyramidal symptoms. Dry mouth, which may be one of the more annoying anticholinergic side effects, occurred more frequently in the group given amitriptyline plus perphenazine. More importantly, more patients in the amitriptyline-perphenazine group than in the amoxapine group had clinically notable tremor and/or rigidity (43% versus 12%, respectively). Although these symptoms were not severe enough to stop medication, their presence could suggest both a potentially disabling acute effect that could lead to noncompliance and a risk factor for the future emergence of dyskinetic symptoms.

It has been clearly demonstrated in vitro (22) that amoxapine, particularly its 7-OH metabolite, can bind to dopamine receptors with a potency similar to that of haloperidol. It is clear that amoxapine can cause an elevation of prolactin, which at least to some degree suggests dopamine blockade, in clinical subjects (24, 25, 31, 32). However, the level of prolactin elevation observed during amoxapine treatment is much less than that observed during treatment with typical neuroleptics, including haloperidol (30).

It has been suggested that the synergistic effect of an antidepressant plus an antipsychotic on the down-regulation of 5-HT_2 binding sites may be related to the treatment efficacy of that combination in psychotic depression (33). Amoxapine may down-regulate 5-HT_2 receptors differently from other antidepressants (34, 35) but similarly to the antipsychotic loxapine (36). Although in vitro studies suggest that these drugs selectively bind to dopamine 1 (D_1) rather than dopamine 2 (D_2) receptors (37), the antipsychotic effect of amoxapine in the treatment of psychotic depression may not occur completely through dopamine blockade. Other mechanisms, such as effects on the serotonin system (which may be linked to the dopamine system), may be operative in the treatment of this illness. In this regard, it appears that amoxapine has binding characteristics at the 5-HT_2 and D_2 receptors that produce a 5-HT_2:D_2 ratio similar to that of a number of atypical antipsychotic compounds (38). Further biological studies using measures of serum prolactin and plasma homovanillic acid measurement as well as measures of treatment response in relationship to serum amoxapine metabolite levels may all help to clarify this issue.

It is clear that amoxapine can cause extrapyramidal side effects (39–41) and dyskinesia (42) in some patients. It is not certain to what extent amoxapine can cause these effects in comparison with neuroleptics during the treatment of psychotic depression. Although emergence of extrapyramidal symptoms in the present study appeared greater in the amitriptyline-perphenazine group, both medication regimens should be used with the understanding of the risks involved.

In summary, amoxapine appears to effect a response rate similar to that of a combination of amitriptyline plus perphenazine in the treatment of major depression with psychotic features. Both medication regimens were equally tolerated by our patients. Of potential clinical importance, the combination of amitriptyline plus perphenazine caused more frequent extrapyramidal side effects. Since amoxapine is a single agent with a unique pharmacological profile that may involve

both selective dopamine receptor binding and 5-HT$_2$ effects, it should be considered an alternative treatment for major depression when psychotic features are present.

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A Controlled Trial of Fluvoxamine
in Obsessive-Compulsive Disorder:
Implications for a Serotonergic Theory

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Thirty-eight patients with primary obsessive-compulsive disorder participated in a 10-week, double-blind, placebo-controlled trial of the potent, selective serotonin reuptake inhibitor fluvoxamine. Fluvoxamine was significantly better than placebo on two of three measures of improvement in obsessive-compulsive symptoms. The authors also compared studies of the serotonergic agents fluvoxamine, sertraline, fluoxetine, and clomipramine and found that a greater effect size was associated with less serotonergic specificity and that some ability to affect other neurotransmitter systems may be a necessary but not sufficient requirement for antiobsessional activity. These data lend only partial support to a serotonin hypothesis of obsessive-compulsive disorder.
(Am J Psychiatry 1990; 147:1209–1215)

E ven though we can effectively treat many patients with obsessive-compulsive disorder with combinations of medication and behavior therapy, some patients remain refractory to conventional therapies. Although occasional patients respond to a variety of drugs, the most predictably helpful agents are the antidepressant drugs (1, 2). Those antidepressants which specifically affect brain serotonergic systems seem to be particularly effective in improving symptoms of patients with obsessive-compulsive disorder (1, 2). Results of double-blind, placebo-controlled trials of clomipramine (3–9) and fluvoxamine (10, 11), as well as open trials of fluvoxamine (12) and fluoxetine (13–15), suggest the efficacy of these serotonergic agents. In addition, other studies using direct serotonergic agonists, such as metachlorophenylpiperazine, and serotonergic antagonists, such as metergoline, suggest that brain serotonergic systems may be intimately involved in the pathogenesis of obsessive-compulsive disorder (16, 17).

Goodman et al. (10) reviewed the evidence for and against the involvement of a drug's serotonergic properties in improving symptoms of obsessive-compulsive disorder. They concluded that clomipramine's success in treating obsessive-compulsive disorder may not be due entirely to its inhibitory effects on serotonin uptake, since desmethylclomipramine, the main metabolite of clomipramine, potently blocks reuptake of norepinephrine as well as serotonin (10). Levels of desmethylclomipramine are generally higher in plasma than the parent compound. In support of the importance of the serotonergic properties of clomipramine in affecting symptoms of obsessive-compulsive disorder, several studies have reported a significant correlation between beneficial effects and plasma levels of clomipramine (7, 18) but not levels of desmethylclomipramine (7, 18).

CSF studies of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and analyses of platelet serotonin content provide further evidence that the serotonergic properties of clomipramine may be related to its efficacy in obsessive-compulsive disorder. Thoren et al. (4) found that patients who responded to clomipramine had higher baseline CSF levels of 5-HIAA than did nonresponders and that the degree of improvement in symptoms of obsessive-compulsive disorder during clomipramine treatment was significantly correlated with drug-induced decrease in CSF 5-HIAA level. In another clomipramine trial in adolescents (19), improvement in symptoms of obsessive-compulsive disorder was significantly correlated with pretreatment platelet serotonin concentrations and with clomipramine-induced decrease in platelet serotonin content.

Further support for the serotonergic theory comes from reports that other drugs which affect brain serotonin are sometimes efficacious in the treatment of ob-

sessive-compulsive disorder. In addition to the serotonergic antidepressants already mentioned, these drugs include tryptophan, alone (20) or in combination with clomipramine (21), lithium carbonate (21–24), trazodone (25, 26), and monoamine oxidase inhibitors (MAOIs) (27, 28).

It appears, however, that not all serotonergic drugs are equally effective in treating patients with obsessive-compulsive disorder. Sertraline, a highly specific serotonergic agent, was not as effective as other serotonergic agents have been in reducing obsessive-compulsive symptoms in a placebo-controlled trial in 19 patients (29). Also, buspirone, another drug with partial serotonergic agonist properties, in an open trial in 10 patients with obsessive-compulsive disorder (30), had no overall effect on obsessive-compulsive disorder, depression, or anxiety. This may not be surprising because buspirone is a partial agonist at $5-HT_{1A}$ receptors (31) but ineffective at postsynaptic $5-HT_2$ receptors (32). Since $5-HT_{1A}$ receptors function as inhibitory autoreceptors, buspirone acts to decrease activity in serotonin neurons.

The recent development of drugs with more specific effects on brain serotonergic systems has permitted closer examination of the relevance of a drug's serotonergic properties to its efficacy as an antiobsessional agent (10). For example, zimelidine, a bicyclic antidepressant agent that selectively blocks serotonin reuptake, reduced symptoms of obsessive-compulsive disorder in three (33–35) of four studies (33–36).

In an effort to examine further whether the selective serotonergic properties of a drug confer it with antiobsessional efficacy, we present the results of a double-blind, placebo-controlled trial of fluvoxamine in 38 patients with obsessive-compulsive disorder. Fluvoxamine is an experimental serotonergic agent that has been shown to be an effective antidepressant agent when compared in double-blind trials with clomipramine (37) and imipramine (38–40). There is also evidence that fluvoxamine, which is a unicyclic agent that also possesses selective and potent effects on serotonin reuptake inhibition, may be helpful in the treatment of severe obsessive-compulsive disorder (10–12). In one open trial (12), six of 10 inpatients experienced clinically significant improvement, and in a controlled trial (10), nine of 21 patients with obsessive-compulsive disorder were much improved with fluvoxamine and none responded to placebo. This earlier controlled trial of fluvoxamine in obsessive-compulsive disorder did not allow an adequate assessment of its antiobsessional effects separate from its antidepressant effects, since about half of the patients in this report had concurrent major depression (10). Also, the treatment duration in this study was shorter than the 10 weeks usually required in trials of patients with obsessive-compulsive disorder; the first 18 analyzable patients participated in only 6 weeks of double-blind treatment, and the next 24 analyzable patients received 8 weeks of double-blind treatment. During this study, in addition to treatment with placebo or fluvoxamine,

patients also attended individual psychotherapy sessions once a week; here they were encouraged to resist their obsessions and compulsions.

In our present study of the efficacy of fluvoxamine in patients with obsessive-compulsive disorder, no other treatments were allowed, depressed patients were excluded, and the double-blind portion of the study was continued for a full 10 weeks in all patients.

METHOD

After giving informed consent and discontinuing all psychotropic medications for 2 weeks, 40 patients entered a 2-week, single-blind placebo washout period; 38 of these patients completed the study. All subjects were outpatients and met *DSM-III* criteria for obsessive-compulsive disorder, had had symptoms of obsessive-compulsive disorder for at least 1 year, and were not depressed according to clinical interview. To ensure that patients had substantial obsessive-compulsive disorder symptoms, a minimum score of 7 on the National Institute of Mental Health (NIMH) Global Obsessive-Compulsive Scale (7) was required for entry into the study. No patient met *DSM-III-R* criteria for major depression according to clinical interview, and each patient had a baseline 17-item Hamilton Rating Scale for Depression (41) score of less than 20 as well as a score of 2 or less on item 1 (depressed mood) of this scale. (Baseline was the end of the 2-week washout period.) Patients with a history of other psychiatric disorders (schizophrenia, psychotic symptoms, bipolar affective disorder, organic mental disorder, psychosurgery, personality disorder that might interfere with compliance, Tourette's disorder, panic disorder, agoraphobia, eating disorders, substance abuse, or alcoholism) within 1 year were excluded from the study. Pregnant or lactating women as well as women of childbearing potential who were not taking adequate contraceptive measures were also excluded. A negative serum pregnancy test was required before entry into the study.

All patients were free of unstable medical disorders, including cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, endocrine, or hematologic illnesses. All patients were chemically euthyroid during the study. No patient had taken MAOIs, anxiolytics, antipsychotic agents, or lithium within 4 weeks of drug allocation, and none had taken other antidepressant agents within 2 weeks of drug allocation. None of the patients had ever received depot neuroleptics, and none had been psychiatrically hospitalized or received ECT within 6 months before entry into the study. The patients' previous unsuccessful treatments are listed in table 1.

All patients gave a complete medical and psychiatric history and were given a physical examination before entry into the study. All patients received one placebo capsule single-blind each evening at bedtime during the 14-day washout period. Eighteen subjects were then

TABLE 1. Previous, Unsuccessful Treatments of 38 Patients With Obsessive-Compulsive Disorder Given Fluvoxamine or Placebo[a]

Previous Treatment	Patients Given Fluvoxamine (N=18)	Patients Given Placebo (N=20)
None	0	3
Psychotherapy	7	8
Behavior therapy	2	6
Medications	15	17
All cyclic antidepressants other than those listed below	10	8
Clomipramine	3	0
Sertraline	1	4
Fluoxetine	3	2
Maprotiline	2	0
Trazodone	2	2
Monoamine oxidase inhibitors	2	6
Lithium carbonate	5	0
Benzodiazepines	7	6
Synthroid	1	0
Neuroleptics	3	5
Ergot mesylates	1	0
Methylphenidate	1	0
Clonidine	1	0
Buspirone	2	1

[a]Most patients had been given more than one type of treatment.

randomly assigned to fluvoxamine (50 mg) and 20 to identical-appearing placebo capsules for the 10-week, double-blind study period. After drug allocation, patients were instructed to take their medication at bedtime during the first week and twice daily (i.e., morning and bedtime) thereafter. The drug doses were titrated up to 300 mg/day of fluvoxamine over a 2–3-week period according to the patients' tolerance for the drug. Compliance was assessed by pill count at each visit. No other psychotropic medication was given throughout the study, and patients were not permitted to have behavior therapy.

Nine of the 18 patients given fluvoxamine and 11 of the 20 patients given placebo were men; nine of the patients in each group were women. The mean±SD age of the fluvoxamine group was 37.5±9.3 years; for the placebo group it was 34.6±12.9. The mean±SD age of all 38 patients was 35.9±11.3 years (range=20–68). The mean age at onset of obsessive-compulsive disorder of the fluvoxamine group was 17.6±9.7; that of the placebo group was 17.3±10.6. The patients in the fluvoxamine group had had the illness for 20.3±11.1 years; the patients in the placebo group had had it for 17.8±7.6 years. The initial score of the fluvoxamine group on the Hamilton depression rating scale was 7.7±5.9; for the placebo group it was 7.5±6.2. The two groups did not differ significantly in any of these characteristics according to chi-square analysis.

At each assessment point in the study, patients underwent measurement of vital signs and routine laboratory tests, including hematologic profile, serum chemistries, and urinalysis. An ECG was performed before baseline and at the end of the study. At each scheduled visit, patients were asked whether they had

experienced any unusual or unwanted signs or symptoms.

Patients were assessed by experienced raters (either a psychiatrist [M.A.J., P.S., or L. Buttolph]or a doctoral-level psychologist [L. Baer or W.E.M.]) at baseline and after 2, 4, 6, 8, and 10 weeks on medication or placebo. The principal measure of outcome was the Yale-Brown Obsessive-Compulsive Scale (42, 43). The same rater assessed each individual patient throughout the course of the study.

The Yale-Brown Obsessive-Compulsive Scale has been used as the main dependent variable in multicenter trials of clomipramine and sertraline and has demonstrated reliability and validity (42, 43). It is a 10-item semistructured questionnaire with each item scored on a 5-point scale from 0 (least symptomatic) to 4 (most symptomatic) so that the total score (sum of items 1 through 10) ranges from 0 to 40. The raters used in our study were provided with standardized instructions in the use of the Yale-Brown Obsessive-Compulsive Scale, and they demonstrated excellent interrater reliability, with an intraclass correlation coefficient of r=0.96 (p<0.001).

The Yale-Brown Obsessive-Compulsive Scale was designed specifically to rate the severity of obsessions and compulsions and excludes questions about depression or anxiety not directly related to obsessive-compulsive symptoms. Obsessions and compulsions are rated for 1) time occupied by symptoms, 2) interference due to symptoms, 3) distress from symptoms, 4) how much symptoms are resisted, and 5) how much control the patient has over the symptoms. The obsession subtotal of the scale is derived from the sum of items 1 through 5 (range=0–20), and the compulsion subtotal is derived from the sum of items 6 through 10 (range=0–20). The mean decrease in total Yale-Brown Obsessive-Compulsive Scale score from baseline was used as the main outcome measure of response of obsessive-compulsive symptoms to treatment.

In addition to the Yale-Brown Obsessive-Compulsive Scale, the patients were given the NIMH Global Obsessive-Compulsive Scale (7) and a clinician-administered Clinical Global Impression (CGI) of symptoms of obsessive-compulsive disorder.

RESULTS

Thirty-eight of the original 40 patients completed the study. Their mean maximum dose of fluvoxamine was 294 mg/day; 17 of the 18 patients who received fluvoxamine reached the maximum dose of 300 mg; one could tolerate only 200 mg/day. The side effects experienced by the patients are listed in table 2; nine patients had no side effects. Overall, fluvoxamine had no serious side effects, and there were no clinically significant alterations in physical examination, laboratory findings, ECGs, blood pressure, or pulse in any of the patients during the course of the study.

The mean±SD scores of the two groups of patients

TABLE 2. Side Effects Experienced by 38 Patients With Obsessive-Compulsive Disorder Given Fluvoxamine or Placebo

Side Effect	Patients Given Fluvoxamine (N=18)	Patients Given Placebo (N=20)
Insomnia	7	1
Constipation	3	2
Nausea/heartburn	5	2
Fatigue	5	3
Sexual dysfunction	3	1
Tremor	1	0
Headache	5	3
Dry mouth	1	0
Mood swings	0	1
Irritability	1	1
Increased appetite	1	0
Decreased appetite	1	2
Dizziness	3	0
Sour or metallic taste	2	0
Others	5	6
None	2	7

on the three outcome measures at each assessment period are given in table 3. There were no significant differences between the groups at week 0 (baseline) on the Yale-Brown Obsessive-Compulsive Scale (t=0.0, df=36, p=0.98), the NIMH Global Obsessive-Compulsive Scale (t=0.2, df=36, p=0.88), or the CGI (t=0.0, df=36, p=0.98).

For each of the three outcome variables, two-factor repeated measures analyses of variance (ANOVAs) were conducted with the Group factor consisting of drug versus placebo and the Time factor consisting of weeks 2, 4, 6, 8, or 10.

On the Yale-Brown Obsessive-Compulsive Scale, since the Group by Time interaction was significant (F=2.7, df=4, 144, p=0.03), ANOVAs for simple main effects were conducted at each week. Using a conservative alpha level of p<0.01, we found that the groups significantly differed only at week 10 (see table 3). The Group by Time interaction was also significant on the NIMH Global Obsessive-Compulsive Scale (F=3.1, df=4, 144, p=0.02); using the same conservative alpha level, we found that tests of simple main effects showed significant differences between the groups only at weeks 8 and 10 (see table 3). On the CGI, the Group by Time interaction (F=0.6, df=4, 144, p=0.66) and the Group factor (F=3.0, df=1, 36, p=0.09) were both nonsignificant, indicating no differences between the groups on this measure. All significant differences favored the fluvoxamine group over the placebo group. In the patients given fluvoxamine, improvement on the Yale-Brown Obsessive-Compulsive Scale was not significantly correlated with the baseline Hamilton depression score (r=0.21, n.s.).

With a total number of 38, statistical power to detect a "large" effect size (44) was 0.65; our past experiences with similar medications have yielded "large" effects (45). This statistical power is lower than the standard criterion of 0.80 (44).

DISCUSSION

Clomipramine is the most studied drug with demonstrated efficacy in obsessive-compulsive disorder; a number of patients, however, suffer side effects from clomipramine that sometimes limit its long-term use. This study adds to the growing body of evidence that other antidepressants which selectively inhibit serotonin reuptake may also be effective for some patients with obsessive-compulsive disorder. To our knowledge, this is the first published systematic investigation of the use of fluvoxamine in obsessive-compulsive disorder that controlled for depression, used a lengthy study period, and eliminated confounding effects of other types of concomitant therapy. As Charney et al. (17) noted, additional drug efficacy studies involving medications with effects on a variety of neurotransmitter systems are required to determine whether an ability to enhance serotonergic neurotransmission is necessary for a drug to have potent antiobsessional activity. More refined investigations of serotonin receptor sensitivity in untreated and treated patients with obsessive-compulsive disorder are difficult to conduct because of the lack of highly selective agonists and antagonists for the multiple known serotonin receptor types and subtypes.

A guiding concept in the search for psychotherapeutic agents has been that increasing selectivity of drugs for action on a single neurotransmitter system or a single receptor type is desirable. Such highly selective drugs might have fewer unwanted effects such as the anticholinergic effects of the cyclic antidepressants. The unstated and largely untested assumption is that absolute selectivity is also consistent with therapeutic effectiveness. Given the complex interactions among monoaminergic and other neurons in the brain and the lack of evidence that the pathophysiology of obsessive-compulsive disorder or other major psychiatric disorders is due to an abnormality in any single transmitter system, it would not be surprising if this assumption were, in fact, untrue. As an example of monoamine interactions, the serotonergic neurons of the raphe nuclei exert an inhibitory effect on noradrenergic neurons of the locus ceruleus (46). Thus, administration of drugs that facilitate serotonergic neurotransmission, such as serotonin reuptake inhibitors, MAOIs, or serotonin precursors such as tryptophan or 5-hydroxytryptophan, can be expected, at least initially, to suppress noradrenergic activity (47). The fact that most cyclic antidepressants (including clomipramine) and MAOIs also facilitate noradrenergic neurotransmission markedly complicates the effects of these agents. What the desirable endpoint is, however, is not known. The meaning of physiological readouts used to screen antidepressant drugs, such as β-adrenergic receptor regulation, is unclear.

Sertraline (48–56) has the greatest selectivity for serotonin reuptake blockade of any antidepressant yet tried for obsessive-compulsive disorder. Preliminary data indicate that it is not as effective as other sero-

TABLE 3. Clinical Scores at 2-Week Intervals of 38 Patients With Obsessive-Compulsive Disorder Given Fluvoxamine or Placebo

Scale and Time	Patients Given Fluvoxamine (N=18)		Patients Given Placebo (N=20)		Comparison	
	Mean	SD	Mean	SD	F	p
Yale-Brown Obsessive-Compulsive Scale						
Week 0	22.6	3.5	22.7	6.1	—[a]	—
Week 2	21.2	3.8	21.2	6.4	1.4[b]	0.25
Week 4	20.4	4.0	21.2	7.0	2.7[b]	0.11
Week 6	19.2	4.6	21.2	6.5	5.0[b]	0.03
Week 8	18.2	3.5	21.0	6.7	6.9[b]	0.01
Week 10	18.8	4.0	21.8	7.6	20.5[b]	<0.001
NIMH Global Obsessive-Compulsive Scale						
Week 0	8.7	1.4	8.8	1.7	—[a]	—
Week 2	8.5	1.4	8.4	2.0	1.8[c]	0.18
Week 4	7.7	0.8	8.0	2.0	3.9[c]	0.05
Week 6	7.6	1.0	8.1	2.2	5.7[c]	0.02
Week 8	7.1	1.1	8.0	2.0	9.3[c]	<0.01
Week 10	6.8	1.2	8.0	2.2	13.2[c]	<0.001
CGI						
Week 0	4.6	0.6	4.6	0.8	—[a]	—
Week 2	4.4	0.7	4.6	0.8	—[a]	—
Week 4	4.3	0.5	4.8	1.5	—[a]	—
Week 6	4.1	0.5	4.6	1.1	—[a]	—
Week 8	4.0	0.5	4.4	1.0	—[a]	—
Week 10	3.9	0.5	4.4	1.0	—[a]	—

[a]There were no significant effects on this measure.
[b]df=1, 24.
[c]df=1, 55.

tonergic drugs (29), consistent with the idea that drugs with mixed neurotransmitter activities are more likely to be effective. The multicenter controlled trial of sertraline (57), however, found it to be significantly better than placebo in the treatment of patients with obsessive-compulsive disorder. The growing evidence that clomipramine and fluoxetine and now fluvoxamine are at least partially effective in the treatment of patients with obsessive-compulsive disorder lends support to the hypothesis that a necessary but not sufficient property of an antiobsessional agent is facilitation of serotonin neurotransmission. Fluvoxamine is a potent serotonin reuptake inhibitor, and both preclinical and clinical studies indicate that long-term administration of fluvoxamine results in enhancement of serotonergic function (10, 58); however, there is preclinical evidence that chronic fluvoxamine administration has effects on other neuronal systems. In rats, a coupling between fluvoxamine's effects on serotonergic and adrenergic systems has been demonstrated (37).

The medications currently being used to treat obsessive-compulsive disorder can be arranged in decreasing order of selectivity for inhibition of serotonin reuptake; they are, from most to least selective (48, 53), sertraline, fluvoxamine, fluoxetine, and clomipramine. An ex vivo paradigm has been used to show that these agents selectively inhibit serotonin uptake in the brain after systemic administration (48, 53). Relative potencies of these agents have been assessed by measuring serotonin uptake into synaptosomes prepared from

TABLE 4. Measures of Effect for Trials of Four Serotonergic Antidepressants

Antidepressant	Relative Potency[a]	Relative Selectivity of Serotonin Versus Norepinephrine[b]	Effect Size[c]
Sertraline	1.00	21.0:1	0.80
Fluvoxamine	0.38	3.5:1	1.09
Fluoxetine	0.28	2.7:1	1.34
Clomipramine	0.17	1.1:1	1.53

[a]Relative potency of ex vivo inhibition of 5-HT uptake into rat brain synaptosomes (49, 54).
[b]Median inhibitory concentration ratio; in vitro inhibition of monoamine uptake into rat brain synaptosomes (49, 54).
[c]Calculated as baseline mean minus end of study mean divided by standard deviation for the four different trials.

sacrificed rats that had been pretreated by intraperitoneal injection with one of these serotonergic agents before death. With this ex vivo procedure, a hierarchy of relative potencies and selectivities can be determined for each of these serotonergic agents (see table 4). Caution must be exercised, however, in extrapolating data from rat brain models to humans, and conclusions can be considered only tentative.

To date there are no controlled trials comparing the relative efficacy of these medications in obsessive-compulsive disorder. However, our research unit has recently conducted controlled or open trials with each of these medications (9, 15, 29), and we used the meta-

analytic method of calculating effect sizes to compare different studies. Although meta-analysis is a controversial technique (59), it has provided important comparative information in the absence of controlled studies (60). The within-treatment effect size statistic is calculated (for subjects in the active drug group only in controlled studies) as the baseline mean minus the end of study mean divided by the standard deviation. The results of such an analysis of our four studies is summarized in table 4, illustrating that those medications thought to be more selective for serotonin reuptake produced smaller effect sizes. These preliminary data suggest that facilitation of serotonergic neurotransmission may be necessary but is not sufficient for effective treatment of patients with obsessive-compulsive disorder; that is, pure serotonergic agents may be less effective treatments than drugs which also have some effects on other transmitter systems (e.g., norepinephrine).

With only one effect size per medication it is not possible to construct confidence intervals to perform a statistical meta-analysis (60). However, given our four studies, with 24 possible permutations, the likelihood of this order occurring by chance is less than 0.05. Consistent with our findings, another center in the clomipramine trial (45) found an effect size of 1.84. Although suggestive, interpretation of these effect sizes is limited for a number of reasons: studies were drawn from different samples, the fluoxetine trial was open, and a single effect size can be influenced by size of a group's standard deviation and baseline level of symptoms of obsessive-compulsive disorder.

In summary, according to our meta-analysis of four studies performed by the same investigators of the serotonergic agents fluvoxamine, sertraline, fluoxetine, and clomipramine in obsessive-compulsive patients, it appears that among agents with selective and potent effects on serotonin reuptake, greater effect size is associated with less serotonergic selectivity. These data do not support a hypothesis that the serotonergic system is the only neurotransmitter system involved in the pathophysiology of obsessive-compulsive disorder; the role of other neurotransmitter systems in this disorder needs to be further explored.

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Alexithymic Features in Relation to the Dexamethasone Suppression Test in a Finnish Population Sample

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Hypothesizing that a positive DST result could reflect an aberrant stress reaction in subjects with alexithymic features, the authors investigated the relationship between alexithymic features and DST results in 266 subjects from a Finnish adult population sample. Alexithymic features were assessed with the Beth Israel Questionnaire. The authors found a statistically significant association between observed alexithymic features and a positive DST result. This association could be seen after adjustment separately for age, social rank, marital status, and the occurrence of depression.
(Am J Psychiatry 1990; 147:1216–1219)

A lexithymia is a concept based on clinical observation of psychosomatic patients; the word was coined by Sifneos in 1972 (1). It means limited ability to express emotions verbally and, more generally, impoverished fantasy life and lack of imagination. Observations of the same phenomena were published before Sifneo's work, e.g., by Ruesch in 1948 (2).

Although alexithymia has been used widely as a clinical concept, there has been abundant discussion of its theoretical basis and definition. The measurement of alexithymia has commonly been considered as problematic, e.g., by Lesser (3). Various theories about the origin of alexithymia have been proposed and range from neurophysiological (4) and genetic (5, 6) to developmental (7) and psychodynamic (8). The central question is, Is alexithymia a constant (trait) or a varying, situation-dependent phenomenon (state) or both? Each alternative has been supported (9, 10). Recently opinions favoring a broad etiology for alexithymia seem to have gained support, as has the view of alexithymia as a spectrum disorder rather than an all-or-none phenomenon. At the same time, the exact definition of the alexithymia concept has become even more difficult (11).

Studies on alexithymia have almost entirely involved various patient samples. To our knowledge, nothing has been published concerning the prevalence of alexithymia or its possible correlates in any unselected population sample (12).

The dexamethasone suppression test (DST) has been extensively studied as a method of diagnosis and treatment follow-up in depression. According to the data gathered in recent studies, the clinical usefulness of the DST for these purposes is poor (13–15). Recently it has been proposed that a given biological abnormality (such as the nonsuppression of cortisol in the DST) is probably related to a specific disturbance of behavior rather than, for example, depression as such (16). A positive DST result (nonsuppression of cortisol) could then reflect an exceptional stress reaction.

Alexithymia and stress have also been connected on a theoretical basis (17), and the theory has been supported by some empirical studies (18, 19). According to these, alexithymic features are related to sympathetic overreactivity.

The purpose of this study was to find out possible associations between alexithymic features and nonsuppression of cortisol in the DST in a population sample. We hypothesized that a positive DST result reflects an aberrant stress reaction in people who have difficulties in expressing emotional stress verbally, i.e., people with alexithymic features.

METHOD

The sample for this study was obtained from persons participating in the 16-year follow-up of a Finnish psychiatric epidemiological study of the general population (20). The initial sample consisted of 500 persons aged 15 to 64 years, and it was stratified so that each 10-year age group was represented by the same number of subjects. At the beginning of the follow-up, 430 of these persons were still alive, and 266 participated in the present study, so the response rate was 62%. The group consisted of 138 women and 128 men aged 31 to 81 (mean±SD age=52.9±12.6 years).
The whole examination set, including the DST, was

performed for 261 persons (135 women and 126 men); for five persons the DST was not performed, but they were assessed in relation to alexithymic features. The subjects were fully informed about the nature of the study procedure, which had been approved by the Ethical Committee of the Rehabilitation Research Center, and consent was obtained from each subject before the study.

The assessment of alexithymic features was made by researchers blind to the DST result. It was based on the Beth Israel Questionnaire (1), which yields a score of 0 to 8 points. The subjects' scores were divided into three categories: 0–2=no alexithymia, 3–5=mild alexithymic features, 6–8=alexithymia proper. For some analyses the categories of mild alexithymic features and alexithymia proper were combined.

The DST was performed as follows: on day 1, 1 mg of dexamethasone was given orally at 11:00 p.m. On day 2, blood samples for determination of serum cortisol levels were obtained at 3:30 p.m. Serum cortisol concentrations were assayed in duplicate by means of radioimmunoassay with a commercial radioimmuno-assay kit (Cortisol-^{123}I, Farmos Diagnostica, Finland). For serum cortisol levels, the interassay coefficients of variation for high and low serum pools in 16 consecutive runs were 7.8% and 8.6%, respectively. The intra-assay coefficients of variation for high and low values were 9.0% and 7.0%, respectively. Subjects with serum cortisol concentrations of 140 nmol/liter or more were categorized as nonsuppressors.

To determine the social rank of each subject, the nine-step scale of Rauhala (21) was used. It is based on the social valuation of occupations (1=highest, 9=lowest).

The occurrence of depression was determined with the CATEGO computer program for the full version of the Present State Examination (PSE) (22), which was a part of the psychiatric interview used in the study.

The frequency tables were analyzed by means of the chi-square test or Fisher's exact test. Because of some skewed distributions, Spearman's correlation coefficient was used instead of the Pearson correlation. Adjusted relative risks were based on the logistic regression model with one confounding factor. The statistical significance is expressed in exact p values except in the case of very small p levels.

RESULTS

Of the 266 total subjects, 11 (4.1%) had alexithymia proper (Beth Israel Questionnaire score=6–8) and 58 (21.8%) had mild alexithymic features (score=3–5). The prevalence of alexithymia proper was 1.4% in women and 7.0% in men, and the prevalence of mild alexithymic features was 18.8% in women and 25.0% in men. A positive DST result (nonsuppression) was found in 37 subjects altogether (14.2%), 18 women (13.3%) and 19 men (15.1%).

The percentage of positive DST results increases .

TABLE 1. Relation of DST Results to Beth Israel Questionnaire Alexithymia Scores in a Finnish Population Sample

| Beth Israel Questionnaire Category | N | Postdexamethasone Cortisol Level | | | |
| | | ≥140 nmol/liter | | <140 nmol/liter | |
		N	%	N	%
No alexithymia (score=0–2)	195	20	10.3	175	89.7
Mild alexithymic features (score=3–5)	55	11	20.0	44	80.0
Alexithymia proper (score=6–8)	11	6	54.5	5	45.5
Total	261	37	14.2	224	85.8

clearly with increasing alexithymic features (table 1). When the group of subjects with alexithymia proper was compared to the rest of the sample, the difference in positive DST results was statistically significant (p=0.001, Fisher's exact test, two-tailed). The proportion of positive DST results in the subjects with either mild alexithymic features or alexithymia proper was 25.8%. The difference in positive DST results between this group and the group without alexithymia was also statistically significant (p=0.004, Fisher's exact test, two-tailed).

The relationship between alexithymia scores and postdexamethasone serum cortisol levels was also examined by means of correlation: the Spearman's correlation coefficient was 0.17 (df=259, p=0.005).

Positive DST results did not correlate with the occurrence of clinical depression. According to the PSE-CATEGO, 17 of the subjects had a depressive disorder (neurotic depression, N=13; retarded depression, N=4). Of these 17, only one subject (5.9%), with neurotic depression, had a positive DST result.

Because the correlation between the alexithymia scores and DST results was possibly due to variables correlating with both the alexithymia scores and DST results, it was necessary to examine this result more closely. Both the alexithymia scores and DST results were examined separately in relation to certain sociodemographic variables. These are presented in table 2. For the alexithymia scores, age was the most significant factor; there was a clear increase of alexithymia and alexithymic features with increasing age (x^2=24.51, df=3, p<0.001). The prevalence of alexithymia or alexithymic features was higher in men than in women (x^2=4.77, df=1, p=0.03), higher for the lower social ranks (x^2=6.10, df=2, p=0.05), and higher in single subjects than in those living in marital or marital-like relationships (x^2=5.32, df=1, p=0.02).

Table 2 also shows the distribution of DST results by the same sociodemographic categories. The DST results were not significantly associated with sex (x^2=0.16, df=1, p=0.69) or age (x^2=4.70, df=3, p=0.20), although the prevalence of positive DST results in-

TABLE 2. Relation of Beth Israel Questionnaire Alexithymia Scores and DST Results to Sex, Age, Social Rank, and Marital Status in a Finnish Population Sample

Variable	N	No Alexithymia (score=0–2) N	No Alexithymia (score=0–2) %	Mild Alexithymic Features or Alexithymia Proper (score=3–8) N	Mild Alexithymic Features or Alexithymia Proper (score=3–8) %	DST Result N	Cortisol Level ≥140 nmol/liter N	Cortisol Level ≥140 nmol/liter %	Cortisol Level <140 nmol/liter N	Cortisol Level <140 nmol/liter %
Sex										
Female	138	110	79.7	28	20.3	135	18	13.3	117	86.7
Male	128	87	68.0	41	32.0	126	19	15.1	107	84.9
Age (years)										
31–40	55	52	94.5	3	5.5	54	5	9.3	49	90.7
41–50	66	54	81.8	12	18.2	64	6	9.4	58	90.6
51–64	92	60	65.2	32	34.8	91	18	19.8	73	80.2
≥65	53	31	58.5	22	41.5	52	8	15.4	44	84.6
Social rank[a]										
1–3	18	17	94.4	1	5.6	18	0	0.0	18	100.0
4–6	159	120	75.5	39	24.5	156	17	10.9	139	89.1
7–9	89	60	67.4	29	32.6	87	20	23.0	67	77.0
Marital status										
Single	72	46	63.9	26	36.1	70	15	21.4	55	78.6
Dyadic	194	151	77.8	43	22.2	191	22	11.5	169	88.5
Total	266	197	74.1	69	25.9	261	37	14.2	224	85.8

[a]According to scale of Rauhala (21); 1=highest rank, 9=lowest.

TABLE 3. Adjusted Relative Risks of Alexithymia or Alexithymic Features in Subjects With Positive DSTs in a Finnish Population Sample[a]

Confounding Variable	Adjusted Relative Risk	χ^2	df	p
Age	1.73	5.73	1	0.02
Social rank	1.95	6.73	1	0.009
Marital status (single versus dyadic)	2.17	7.52	1	0.006
Depression (PSE-CATEGO)	2.21	8.75	1	0.003

[a]Logistic regression model.

creased somewhat with increasing age. There were more positive DST results in subjects with lower social ranks than in those with higher ranks ($\chi^2=9.91$, df=2, p=0.007) and more among single subjects than among those living in dyadic relationships ($\chi^2=4.14$, df=1, p=0.04).

According to table 2, both alexithymia scores and DST results were associated with social rank and marital status; in addition, alexithymia scores were associated with age. We wanted therefore to examine the association between alexithymia scores and DST results while regarding the other factors as confounding variables. In addition to age, social rank, and marital status, we included depression, as determined with the PSE-CATEGO. The unadjusted relative risk of Beth Israel Questionnaire scores of 3–8 in the DST-positive category was 2.10. The results of adjusting for the confounding variables are presented in table 3. All the adjusted relative risks in table 3 are significant, which means that the association between alexithymic fea-

tures and DST results was not confounded by these factors. There were no significant interactions among these variables (p>0.10 for each variable).

DISCUSSION

The results of our study show a slight, but statistically significant association between observed alexithymic features and a positive DST result in a population sample. To our knowledge, observations on this kind of association have not been published earlier. This association could also be seen after adjustment separately for age, social rank, marital status, and the diagnosis of depression.

Although the number of subjects with alexithymia proper in our sample was small, the observed association was supported by the prevalence of positive DST results in the group with mild alexithymic features, which was twice as high as in the subjects with no alexithymia.

The prevalence of alexithymia proper (4.1%) in our study was of the same magnitude as that reported earlier in nonclinical student populations (23, 24).

The prevalence of positive DST results (14.2%) was somewhat higher than that reported for healthy subjects (7.4%) in a review of 53 studies (25). In our study, the DST was not correlated with the diagnosis of depression. This result is probably influenced by the fact that the majority of depressions in this sample were at the neurotic level.

The measurement of alexithymic features is problematic. We used the Beth Israel Questionnaire, which has probably been used most frequently for measuring

alexithymia (12). Its validity has been criticized (26) but remains acceptable (27–29).

Alexithymia and alexithymic features seem to be associated with lower social rank. A substantial number of the subjects in the lower classes who had alexithymia or alexithymic features showed nonsuppression of cortisol in the DST, which might be a psychophysiological consequence of psychosocial stress.

Our results support but do not prove the hypothesis that a positive DST can reflect an aberrant stress reaction in subjects with alexithymic features. The relatively high prevalence of positive DST results in subjects with alexithymic features may indicate that nonsuppression of cortisol in the DST reflects an aberrant means of handling psychosocial stress or a reaction to a stressful situation. Alexithymic features may be connected with the same phenomenon, i.e., psychic stress that has no channels or only poorly developed channels for proper emotional discharge.

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Commentary

The Coming Crisis in Funding Child Psychiatry Training

Robert S. McKelvey, M.D.

Rapid changes in health care financing and delivery systems will adversely affect child psychiatry training. Reductions in teaching hospitals' patient revenues and in federal support for graduate medical education have made the development of strong academic and research programs more difficult. Training programs must search for innovative ways to fund clinical training if they are to survive and grow. The authors review major sources for funding, such as state governments, future employers of trainees, endowments, faculty practice plans, and residents paying for training, and discuss opportunities for increasing their contributions.

(Am J Psychiatry 1990; 147:1220–1224)

C onsiderable attention has been focused on the nationwide shortage of child psychiatrists and on child psychiatry training programs' inability to attract and educate sufficient numbers of quality residents (1, 2, and address by P. Fink to the National Recruitment Conference in Child Psychiatry, San Diego, 1989). A variety of solutions have been proposed. These focus on increasing child psychiatry's academic attractiveness by promoting greater research productivity and closer ties to academic medical centers and on enlarging child psychiatry's role in the education of medical students and psychiatry residents (1, and address by P. Fink).

As academic child psychiatry searches for ways to become more academic, the health care system is experiencing rapid and dramatic changes in the structure of its remuneration and delivery. Ginzberg (3) sees "the destabilization of health care" as resulting from

three major changes: the loss of physician dominance in medical decision making, hospital chains' erosion of the community hospital's traditional role, and the evaporation of cross-subsidization as a means of funding care for the poor. The growing preoccupation with the runaway costs of health care has fueled the destabilization process. Health maintenance organizations (HMOs), preferred provider organizations (PPOs), diagnosis-related groups (DRGs), preadmission certification, and patient copayment are some of the devices used by payers, both private and public, to reduce "unnecessary" medical expenses. Although medical education represents only 2% of the total health care budget, it too must stand the increasing scrutiny of cost-conscious policy makers, industry leaders, insurance executives, and hospital managers (4). This is exemplified by proposed reductions in Medicare's payments for both the direct and indirect costs of medical education (5). Federal support for psychiatric training through the National Institute of Mental Health (NIMH) has also diminished strikingly. In 1969 $100 million was allocated for mental health training; by 1987 this had fallen to $20 million (6). The Administration's current budget calls for only $7.5 million to be allocated to the NIMH clinical training program (testimony of J. Egan before the Senate Appropriations Subcommittee on Labor, Health, and Human Services, May 11, 1989).

IMPACT OF CHANGE

Dramatic changes in health care financing and delivery systems, along with diminished federal support for clinical training, threaten academic child psychiatry's attempts to increase faculty commitment to research and education and reduce the likelihood that the field will be able to attract more and better residents into its training programs. As an illustration of the complex effects of these changes on child psychia-

TABLE 1. Sources of Funding for the Baylor Child Psychiatry Training Program, 1978–1989

	Percentage					
Funding Source	1978–1979	1980–1981	1982–1983	1984–1985	1986–1987	1988–1989
For faculty						
Baylor funds	38	33	35	33	32	33
Baylor fee income	6	7	8	7	7	7
Texas Children's Hospital	36	54	57	60	61	33
Federal (NIMH)	20	6	—	—	—	—
Cullen Bayou Place (social welfare agency)	—	—	—	—	—	27
For trainees						
Texas Children's Hospital	90	100	100	90	82	15
County (Mental Health-Mental Retardation Authority)	10	—	—	—	—	—
For-profit hospital	—	—	—	10	12	6
Cullen Bayou Place						
Patient revenues	—	—	—	—	—	50
Endowment	—	—	—	—	6	29

try training, in this article I review the past decade's experience of the Division of Child Psychiatry at Baylor College of Medicine. While it is not entirely representative of child psychiatry training programs nationwide in its increasingly heavy reliance on patient revenues for support, our program's situation does highlight the effects of changes in health care financing and delivery systems on clinical education.

Table 1 shows the percentage of funds derived from various sources over the past 11 years to support our faculty and resident stipends. Several trends and developments are worth noting. In 1978 20% of faculty salaries came from federal (NIMH) support. By 1982 this support had been eliminated and had to be absorbed by our sole teaching affiliate at that time, Texas Children's Hospital, a nonprofit, tertiary-care pediatric teaching hospital. Similarly, county support for training was withdrawn at the end of 1979, and this loss was also absorbed by Texas Children's Hospital. Funding these additional training costs did not seem a great burden, for the hospital's profit margin was fairly large. However, several factors during the mid-1980s contributed to substantial erosions of this profit margin and a decision by the hospital's administration to reduce its support for child psychiatry training. These factors may be briefly summarized as follows: Houston's worsening economic condition, a rapid increase in proprietary hospital competition spurred by Texas's removal of the requirement for hospital certificates of need in 1985, and an increasing proportion of poorly remunerative Medicaid patients in the hospital's caseload as better-paying patients were siphoned off either by proprietary hospitals or by an expanding number of managed care plans. In 1986 the administration of

Texas Children's Hospital decided to close the hospital's child psychiatry outpatient clinic, which along with the consultation-liaison service was the major site for child psychiatry training in the Baylor system. Reasons for closing the outpatient clinic were its substantial (approximately $400,000 per year) deficit and a perception that child psychiatrists in the outpatient clinic, as opposed to those on the consultation-liaison service, were not responsive to the needs of the hospital's medical staff.

A search was begun for a suitable relocation site for the outpatient clinic. In 1987 an affiliation agreement was signed between Texas Children's Hospital, Baylor College of Medicine, and Cullen Bayou Place, the mental health division of a large, nonprofit multiservice social welfare agency. In addition to relocating the outpatient clinic to Cullen Bayou Place, the agreement also stipulated the opening of two inpatient teaching units there. It was hoped that profits from these units would help offset the outpatient clinic deficit, as well as satisfy residency review committee requirements for inpatient training in child psychiatry.

Currently, the child psychiatry division consists of 11 full-time faculty members (of whom six are child psychiatrists) and eight child psychiatry residents, along with psychology and social work interns. As can be seen in table 1, funding for faculty salaries is derived from patient revenues (67%), and the medical school (33%). Residents' salaries are derived from patient revenues (71%) and Cullen Bayou Place training endowment income (29%). The program's heavy dependence on patient revenues is typical of residency training programs nationwide (7), although somewhat less typical of child psychiatry programs, which rely more heavily on medical and state government support (1) than ours does.

Our teaching facilities' ability to generate the patient revenues on which our program so heavily depends continues to be strongly influenced by two factors already noted, namely, the removal in Texas of the certificate of need requirement for new hospital construction and the ever-increasing role of managed health care. In addition, with the opening of our free-standing psychiatric hospital units, a third factor—the rapid reduction of insurance benefits for inpatient psychiatric care—has played a major role.

Texas's elimination in 1985 of the certificate of need requirement opened the floodgates to the proprietary hospital chains, which rapidly saturated the Houston market. Between 1978 and 1987, private psychiatric hospital beds of all types increased from 765 to 1,990 (160%). During the same period, beds for children and adolescents increased from 112 to 600 (436%) (8). The vast majority of these beds were in the for-profit sector, making proprietary hospitals the major providers of child and adolescent psychiatric hospital care.

Managed health care—HMOs, PPOs, and self-insured plans—while not as significant in Houston as in other parts of the country, has begun to play a major

role in psychiatric care. With many half-empty psychiatric hospitals bidding aggressively, contracts with managed health care programs have become quite competitive. The result of this competition is lower prices for the same services. For example, on our inpatient unit at Cullen Bayou Place, revenue for care of an HMO patient is only 67% of that for a traditional fee-for-service insured patient, and revenue for a PPO patient is only 80%.

The reduction of inpatient mental health benefits has been equally rapid and dramatic. As an example, Exxon, the area's largest single employer, reduced its cap on inpatient mental health benefits on July 1, 1988, from $1 million (lifetime) to 30 days per calendar year. Policies allowing only brief hospital stays, usually 30 days or fewer, now predominate. Along with excess bed capacity, reduced lengths of stay contribute to lower occupancy rates by requiring more admissions to keep the same number of beds filled.

The result of these three recent and powerful changes in Houston's health care environment—increased competition from proprietary hospitals, the increase in managed health care, and reduced inpatient benefits—has been a steady erosion in our teaching facilities' ability to generate the profits that pay for child psychiatry training. As noted in the Commonwealth Fund's report on academic health centers, "competition on the basis of price and reorganization of medical services to lower costs are beginning to erode the capabilities of academic health centers to fulfill their missions of education, research, and patient care" (4). This is particularly true for specialties, such as child psychiatry, that are not oriented toward procedures (9, 10).

POSSIBLE SOLUTIONS

When we consider ways in which child psychiatry training can expand while revenues in its teaching facilities are falling, it is clear that there is no simple solution. Future funding for child psychiatry training will probably have to come from an extremely creative blending of a variety of sources. Even then, it appears unlikely that sufficient new funding can be found to allow child psychiatry training to continue at its present level.

A review of possible ways to increase funding would include the following sources.

1. Federal and state governments. The severe shortage of child psychiatrists nationally would lead one to expect an increase in federal government support for training. As has been shown, however, the opposite has happened, despite the strenuous efforts of groups such as the American Academy of Child and Adolescent Psychiatry. The "difficult times ahead for graduate medical education" under the Reagan administration, predicted in 1985 by Iglehart (11), are not likely to be reversed by President Bush's administration.

State governments may prove more helpful. They already represent the second largest source of support for child psychiatry training (address by P. Fink, 1989). Support from the states may increase as they work to improve recruitment for state mental health facilities (9). This has, in fact, been true in our area, where a new state hospital staffed by the University of Texas Health Science Center at Houston has allowed its child psychiatry training program to increase faculty and resident positions.

2. Future employers. HMOs, hospital corporations, and private practice groups have long been beneficiaries of child psychiatry training without having to pay for it. Is it reasonable to expect them to help with the expenses of training? Focused as they are on reducing health care costs, HMOs and other managed care providers are unlikely to undertake the added costs of training (12). They might, however, consider funding a particular resident in return for his or her commitment to practice with them for a certain period of time (12). The same may be true for hospital corporations, whose growth can be limited by the supply of psychiatrists and their willingness to use inpatient care (13). Local private practice groups may also show an interest in this approach as new graduates become harder to find. In addition, some proprietary chains have considered affiliation with academic health centers (14, 15). Although the issues in mixing profit and education are complex (15, 16), there is at least one report of a successful collaboration between a child psychiatry training program and a proprietary chain (17). Of course, the for-profit institutions are also beginning to experience the limits of growth (3) and may not wish to commit diminishing profits to training unless this can be shown to increase revenues. In Houston one proprietary hospital, beset by financial difficulties, has withdrawn much of its support for residency training.

3. Charity. The partnership between medical education and hospital charity care has a long history in this country, but in the era when private insurance payments to hospitals increased, nonprofit institutions began to drift away from their charitable roots (3). As patient revenues fall, cross-subsidizing medical education will become more difficult, and nonprofit institutions that support training may increasingly rely on income from endowment and contributions to pay faculty and resident salaries. Our program has had some success in locating endowment funding, which now pays for slightly more than two resident positions. Perhaps it is time for psychiatry departments to hire directors of development.

4. Faculty practice plans. Many psychiatry training programs have faculty practice plans that help defray educational costs. Perkoff (18), writing of graduate medical education in general, suggested that these plans may be a good place in which to look for increased support of medical training. However, as Pardes and Pincus (9) pointed out, the situation may be different for psychiatry because it is not procedure-

based and thus has less revenue-generating capability. Given the current marked salary differentials between academic child psychiatry and the for-profit sector, it is likely that an increased "tax" on faculty practices would simply exacerbate our current problems with faculty recruitment and retention. Also, given the time- and labor-intensive character of psychiatric practice, it is unlikely that one could demand from faculty members both greater patient revenues and greater research productivity.

5. Residents paying for training. In a recent essay on outpatient medical education, Federman (19) quoted from T.F. Harrington's 1905 history of Harvard Medical School: "As the College has not sufficient funds to maintain Professors . . . it would be expedient . . . to elect into those Professorships some gentlemen of public spirit and distinguished ability who would undertake the business . . . for the fees that may be obtained from those who would readily attend their lectures." Is it reasonable to expect child psychiatry residents to pay the cost of their own training? As teaching facilities become more hard pressed, they may demand, along with lower residency stipends, that residents pay their way. This could be accomplished either through careful cost accounting for residents' services or by payments from residents to their training programs. In the former case, an institution might require that a resident deliver sufficient care to offset the cost of his or her support; this might involve working additional hours as care shifts increasingly from hospitals, where physician fees are more fully recoverable, to outpatient care, where collections are less reliable (9). In the latter case, child psychiatry residents, who are usually eligible for full medical licensure and often have completed psychiatry training, would pay for their education, as is now done by psychoanalytic candidates. The question here, similar to the question of more heavily "taxing" faculty, is whether this would further impede recruitment. In certain parts of the country, such as ours, where child psychiatrists' salaries exceed those of general psychiatrists, this may be a viable option. However, where no competitive advantage is gained by extra training, it is hard to imagine why many would choose to undertake it.

CONCLUSIONS

None of the approaches I have outlined offers, either in itself or in combination with others, a complete solution to the problem of funding child psychiatry training in a time of decreasing patient revenues and federal government support. Aside from a reversal in the federal government's recent policies toward clinical training, which seems unlikely, the best prospects for generating new support appear to be in collaborations with state-supported and for-profit institutions, along with efforts to find charitable foundations interested in funding training in a specialty that has a severe short-

age of trainees. In addition, training programs will undoubtedly find themselves under increasing pressure from their teaching facilities to reduce the size of their programs, lower stipends, and require more hours of reimbursable direct service. These constraints will adversely affect recruitment into the field and reduce the number of training slots available.

Ultimately, significant quantitative and qualitative expansion of child psychiatry training programs is impossible without increased federal support. National organizations in both psychiatry and child psychiatry have tried for a number of years to make federal policy makers aware that child psychiatrists are in short supply (2, and testimony of J. Egan, 1989). Judging from the steady reduction in federal support for clinical training, these efforts have encountered limited success. It is likely that federal legislators, perceiving a doctor "glut" and large oversupplies in many specialties, have difficulty separating the problems of one very small specialty from those of the rest of medicine. How can we better highlight our message to them? One possibility is to link child psychiatry training to other, more powerful issues relating to child care, which are receiving considerable attention. We must find allies inside and, particularly, outside of medicine who can support the funding of child psychiatry training as a national priority, along with other efforts to improve the future of our nation's children. In any case, unless the federal government's approach to clinical training in child psychiatry is significantly altered, it is likely that the coming years will find child psychiatrists in still shorter supply.

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Clinical and Research Reports

CSF 5-HIAA and HVA Concentrations in Elderly Depressed Patients Who Attempted Suicide

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CSF findings distinguished 12 elderly depressed patients who attempted suicide from nine depressed patients who did not and from seven normal control subjects. Psychosocial factors and measures of psychopathology did not differentiate suicidal from nonsuicidal patients. Biochemical factors may be important in evaluating suicide risk in the elderly.
(Am J Psychiatry 1990; 147:1225–1227)

T he suicide rate among the elderly steadily increased in the United States during the 1980s. According to the National Center for Health Statistics, in 1986 the suicide rate among those 65 years old and older rose to 21.6 per 100,000, compared with the overall national rate of 12.8 per 100,000. The true rate may be much higher because suicides in the elderly may be masked as accidental overdoses or age-related deaths. Therefore, underreporting may be greater in the elderly than it is in other groups (1). Furthermore, because depression places individuals at higher risk for

suicide throughout the life cycle, elderly depressed patients are at very high risk of suicide (1).

The evaluation of the suicidal patient remains a difficult task for the clinician responsible for assessing this risk (1). The task is made more difficult when evaluating older suicidal patients because the elderly are less likely to communicate their intention to commit suicide than are younger adults (2). In addition, psychosocial risk factors (e.g., recent losses), which may be helpful in determining suicidal risk in younger adults, are of limited value in the elderly because they are more common (3). Finally, the elderly are more likely than younger adults to end their lives when attempting suicide (4); consequently, there is a pressing need for early identification of those elderly patients who are at risk for suicide. For these reasons, new approaches are needed to aid the clinician in identifying the suicidal elderly patient.

A number of studies have reported lower levels of CSF 5-hydroxyindoleacetic acid (5-HIAA) in adult depressed suicidal patients than in diagnostic control subjects (5). Asberg et al. (6) were the first research group to report a greater prevalence of suicide attempts in a group of patients with low levels of CSF 5-HIAA. This relationship was confirmed by Agren (7). A well-designed study by Roy-Byrne et al. (8) failed to confirm the relationship between low levels of CSF 5-HIAA and suicidal behavior, but the preponderance of studies support the relationship between CSF 5-HIAA and suicidal behavior in patients with unipolar depression (5). None of these studies have had elderly patients as their focus.

The purpose of this study was to determine whether elderly patients who attempt suicide differ from elderly patients who do not attempt suicide in biochemical measures of serotonergic function and measures of psychopathology. The study was designed to answer

the following questions: 1) Do elderly patients who have attempted suicide have lower levels of CSF 5-HIAA and homovanillic acid (HVA) than diagnostically and age-matched patients without a history of suicide attempts? 2) Do elderly patients who have attempted suicide have lower levels of CSF 5-HIAA and HVA than normal control subjects matched for age? 3) Do measures of psychopathology (e.g., severity of depression), measures of behavior (e.g., aggression), and psychosocial risk factors (e.g., recent loss or change in marital status) differentiate elderly suicidal patients from elderly nonsuicidal patients?

METHOD

We studied 28 individuals; 21 were psychiatric inpatients (12 with and nine without a history of suicide attempts), and seven were normal control subjects who were recruited from the community. These seven subjects had no history of psychiatric illness or a suicide attempt. All subjects underwent the same screening procedures and were determined to be in good physical health. All of the subjects were 55 years old or older. The mean±SD age of the subjects who had attempted suicide was 63.2±6.8 years; for the patients who had not attempted suicide it was 64.7±7.3; and for the control subjects it was 71.3±6.7. The age differences among the three groups were not statistically significant (F=3.14, df=2, 25, n.s.). The groups were also not significantly different in the proportion of men to women (x^2=1.01, df=2, n.s.); 13 (46%) of the 28 subjects were women. Five of the patients who had and two of the patients who had not attempted suicide had been hospitalized previously. These patients did not differ significantly in the mean±SD number of previous psychiatric admissions; the patients who had attempted suicide had been hospitalized 3.6±2.1 times; those who had not attempted suicide had been hospitalized 4.5±0.71 times (t=0.57, df=5, n.s.).

The Schedule for Affective Disorders and Schizophrenia (SADS) was used to diagnose the patients. The kappa coefficient for interrater reliability on diagnoses was high (0.86). Fifteen (71%) of the 21 patients in this study were diagnosed as having unipolar depression; two were diagnosed as having bipolar disorder, two had an anxiety disorder, and two had a personality disorder.

All patients were hospitalized at the time of the study, and all had been free of psychoactive drugs or any other medications (except for occasional benzodiazepines for sleep) for 14 days before the lumbar puncture. All participants gave written consent after a full explanation of the study.

Measures of psychopathology (the Brief Psychiatric Rating Scale [BPRS] and the Hamilton Rating Scale for Depression) were administered by research psychologists or psychiatrists within 72 hours after the lumbar puncture. We were not able to collect complete psychopathology ratings for all patients. The intraclass

TABLE 1. CSF 5-HIAA and HVA Values of Elderly Depressed Patients Who Did or Did Not Attempt Suicide and Normal Control Subjects

Group	CSF 5-HIAA (ng/ml)[a]		CSF HVA (ng/ml)[b]	
	Mean	SD	Mean	SD
Patients who attempted suicide (N=12)	19.0	6.7	29.9	14.3
Patients who did not attempt suicide (N=9)	25.7	7.3	49.0	21.0
Normal control subjects (N=7)	25.7	4.4	45.5	16.4

[a]There was a significant difference among the three groups (F=3.75, df=2, 25, p<0.05). According to "protected" t tests (10), the differences between patients who did attempt suicide and those who did not (t=2.38, df=25, p<0.02) and between patients who attempted suicide and normal control subjects (t=2.20, df=25, p<0.05) were significant.
[b]There was a significant difference among the three groups (F=3.65, df=2, 25, p<0.05). According to "protected" t tests (10), the differences between patients who did atempt suicide and those who did not (t=2.52, df=25, p<0.02) and between patients who attempted suicide and normal control subjects (t=1.91, df=25, p<0.05) were significant.

correlation coefficient of reliability for the BPRS was 0.80; it was 0.74 for the Hamilton depression scale. Subjects also completed behavioral measures (e.g., the Buss-Durkee Hostility Inventory) and psychosocial measures (the Recent Life Changes Questionnaire). Each patient's medical history, history of aggression, and history of suicide attempts were recorded as well.

CSF was obtained and collected at 9:00 a.m. while the patient was in the lateral decubitus position. Samples of CSF were assayed by using high-pressure liquid chromatography with amperometric detection. Samples were diluted in perchloric acid and aliquots injected directly. The interassay coefficient of variation for this procedure averages 4.6% for 5-HIAA and 5% for HVA (9).

RESULTS

The results of a one-way analysis of variance and follow-up "protected" t tests (10) showed that the mean concentration of CSF 5-HIAA in the elderly patients who had attempted suicide was significantly lower than that of the age-matched group of elderly patients without a history of suicide attempts (see table 1). In addition, the mean concentration of CSF 5-HIAA of elderly patients who had attempted suicide was significantly lower than that of age-matched normal control subjects. Consistent with CSF 5-HIAA results, the mean concentration of CSF HVA of the elderly patients who had attempted suicide was lower than the mean concentration of CSF HVA in the elderly depressed patients without a history of suicide attempts and the normal control subjects (see table 1).

The results of a separate analysis of CSF concentrations in the subgroup of patients with unipolar depression paralleled the findings for the entire group of de-

pressed patients: CSF 5-HIAA levels were lower in patients who had attempted suicide (mean±SD=17.5± 7.1 ng/ml) than in those who had not (26.4±8.2 ng/ml) (t=2.2, df=13, p<0.05). HVA levels were also lower for patients with unipolar disorder who had attempted suicide (23.8±10.2 ng/ml) than for those who had not (46.6±22.8 ng/ml) (t=2.7, df=13, p<0.02). CSF 5-HIAA and HVA concentrations in the total study were highly correlated (r=0.81, df=27, p< 0.001).

These preliminary data did not show significant differences between elderly patients who did attempt suicide and those who did not with regard to measures of history of aggression (t<1, df=12, n.s.) and impulsive behavior (Buss-Durkee Hostility Inventory: t<1, df= 12, n.s.), and measures of psychopathology (BPRS: t< 1, df=11, n.s.; Hamilton depression scale: t<1, df= 15, n.s.). Psychosocial factors (e.g., death of spouse, retirement, problems with physical health), as measured by the Recent Life Changes Questionnaire, did not distinguish the patient groups.

DISCUSSION

This study evaluated the importance of biochemical risk factors and psychological and behavioral risk factors in a group of elderly psychiatric patients, the majority of whom had a diagnosis of depression. Patients who had attempted suicide had significantly lower concentrations of both CSF 5-HIAA and HVA than nonsuicidal patients and normal control subjects. These findings are consistent with the many studies that have reported similar results in the literature on younger adults (5–8). However, we did not detect differences between suicidal versus nonsuicidal elderly patients on psychosocial, psychological, or behavioral measures. This lends support to the idea that psychological factors may be less useful in evaluating suicidal risk in the elderly.

The results of this study underscore the importance of considering the role of biochemical factors, particularly CSF 5-HIAA, in suicidal behavior for the elderly. Because of the small sample size and mixed diagnostic groups, this study is preliminary in nature. However, the biochemical findings are consistent with those of numerous studies in nonelderly subjects. These results suggest the need for a large-scale study of biochemical factors in suicidal behavior among the elderly. Ultimately, research in this area may be of clinical value in the identification of elderly individuals at greatest risk for suicide. It may also aid in the development of pharmacological strategies for treatment of this population.

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A Preliminary Investigation of Alexithymia in Men With Psychoactive Substance Dependence

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The prevalence of alexithymia in a group of newly abstinent male substance abusers (N=44) was 50%. The alexithymic patients had significantly less ego strength and repressive defensive behavior and significantly higher levels of somatic complaints and general dysphoria.

(Am J Psychiatry 1990; 147:1228–1230)

A lexithymia refers to a specific disturbance in emotional processing that is manifested clinically by difficulties in identifying and verbalizing feelings and in elaborating fantasies and by a tendency to focus on and amplify the somatic sensations accompanying emotional arousal (1). While these characteristics were reported initially among patients with "classical" psychosomatic diseases and somatization disorders, they have also been observed in patients with psychoactive substance use disorders (1, 2). It has been hypothesized that substance dependent individuals use drugs or alcohol in an attempt to medicate themselves for certain unpleasant emotional states, which are experienced as unmanageable or overwhelming because of a limited cognitive capacity to differentiate and modulate affects (3, 4). There has been little attempt, however, to investigate empirically the alleged association between alexithymia and substance abuse. Rybakowski et al. (5) reported alexithymia in 78% of a group of male alcoholic inpatients, but the generalizability of this finding is questionable because alexithymia was measured with the Schalling-Sifneos Personality Scale, which has been shown consistently to be neither reliable nor valid (6). More recently, Haviland et al. (7)

used the Toronto Alexithymia Scale, an instrument with demonstrated reliability and validity (6), and found alexithymia in 50.4% of a group of men who were mixed substance abusers.

The purposes of the present study were to further investigate the prevalence of alexithymia among patients with substance use disorders and to examine the relationships between alexithymia and other personality and psychopathology variables in this clinical population.

METHOD

The subjects were 44 men who had been admitted voluntarily to an alcohol and drug abuse inpatient treatment program. Seventeen subjects had histories of chronic alcohol abuse, five had histories of chronic drug abuse, and 22 abused drugs as well as alcohol. The study was preceded by a period of 1 to 7 days of abstinence from alcohol and other addictive chemicals. The subjects' mean age was 37.75 years (range=19–61). All subjects met the *DSM-III-R* criteria for psychoactive substance dependence.

As part of the assessment procedure, all subjects completed the Michigan Alcoholism Screening Test, the Drug Abuse Screening Test, the Beck Depression Inventory, the MMPI, and the Toronto Alexithymia Scale. Using the cutoff score of 74 on the Toronto Alexithymia Scale, we dichotomized the study population into alexithymic and nonalexithymic groups. The two groups were compared on the various measures by two-tailed t tests, with a significance level of $p < 0.05/18$ (Bonferroni correction). The MMPI variables were limited to the 10 clinical scales, the MacAndrew Alcoholism Scale, the Manifest Anxiety Scale, the Ego Strength Scale, and the Repression-Sensitization Scale.

RESULTS

The mean±SD score for the whole cohort on the Toronto Alexithymia Scale was 74.21±12.21. Twenty-two of the 44 subjects scored 74 or higher and were the alexithymic group; the remaining 22 subjects scored 73 or lower and were the nonalexithymic

TABLE 1. Age and Psychometric Test Scores for Alexithymic and Nonalexithymic Male Patients

Variable	Alexithymic Patients (N=22)		Nonalexithymic Patients (N=22)		t (df=42)
	Mean	SD	Mean	SD	
Age (years)	40.6	9.9	35.0	12.2	1.62
Michigan Alcoholism Screening Test	18.5	6.7	16.6	6.6	0.93
Drug Abuse Screening Test	5.5	5.1	9.2	6.4	2.07
MacAndrew Alcoholism Scale	31.0	4.3	30.6	4.5	0.27
Beck Depression Inventory	25.0	9.7	13.3	6.2	4.77[a]
MMPI					
Hypochondriasis	15.6	5.8	9.0	5.5	3.88[a]
Depression	31.5	5.6	24.2	6.6	3.99[a]
Hysteria	26.6	6.3	23.1	4.9	2.07
Psychopathic deviate	28.6	4.6	25.2	5.0	2.37
Masculinity/femininity	27.7	3.8	25.6	4.5	1.72
Paranoia	15.9	4.1	12.6	3.5	2.92
Psychasthenia	29.5	9.7	18.1	8.0	4.20[a]
Schizophrenia	31.1	13.2	18.2	10.3	3.61[a]
Hypomania	22.1	5.3	21.1	5.1	0.66
Social introversion	38.4	7.4	27.8	9.6	4.12[a]
Ego Strength Scale	34.0	5.9	43.4	7.7	4.53[a]
Repression-Sensitization Scale[b]	98.8	22.0	69.6	18.7	4.74[a]
Manifest Anxiety Scale	31.2	8.2	17.6	8.1	5.53[a]

[a]p<0.003.
[b]High scores indicate sensitization and low scores repression.

group. Table 1 compares the mean ages of the two groups and their mean scores for the various measures. The two groups were similar in age and did not differ in relation to the mean severity of dependence as measured by the Michigan Alcoholism Screening Test, the Drug Abuse Screening Test, and the MacAndrew Alcoholism Scale. The alexithymic patients were significantly more anxious and depressed than the nonalexithymic patients and presented more physical complaints and general psychological turmoil. The nonalexithymic patients showed significantly greater ego strength and use of repressive defense mechanisms and were significantly less socially introverted than the alexithymic patients.

DISCUSSION

These results support the clinical impression of a high prevalence of alexithymia among individuals with substance use disorders. The prevalence of 50% is considerably lower than the rate that Rybakowski et al. (5) obtained using an unvalidated measure of alexithymia; however, it is virtually identical to the prevalence reported by Haviland et al. (7) and significantly higher than rates of 35.1% that we have obtained in a group of general psychiatric male outpatients (unpublished data) and 15.4% in a group of normal male adults (8).

Due to the cross-sectional design of the study, we are unable to determine whether alexithymia is an antecedent of substance abuse or a consequence of the disorder or recent abstinence. However, the findings of lower scores on the Ego Strength Scale and higher

scores on the Repression-Sensitization Scale for our alexithymic patients, as well as their significantly higher level of psychological turmoil, support the viewpoint held by many clinicians that alexithymia is a predisposing risk factor for substance abuse and that many addicts use alcohol or drugs adaptively to compensate for defects in affect defense and in the ego's capacity to regulate and modulate emotions and drives (1–4). These psychometric findings are also consistent with the theoretical conception that alexithymic characteristics cannot be attributed to a repressive coping style or excessive use of denial. There are important theoretical differences between the alexithymia construct and the personality dimension of repression-sensitization. However, studies with nonclinical populations have shown that both the Toronto Alexithymia Scale and the Repression-Sensitization Scale correlate negatively with the Ego Strength Scale and that high scorers on either scale (i.e., alexithymic or sensitizing individuals) typically report significantly greater levels of anxiety, depression, and somatic symptoms than low scorers (i.e., nonalexithymic or repressing individuals) (6, 9). Such findings suggest strongly that the higher levels of dysphoria and physical symptoms found in our alexithymic patients are unlikely to be a cause of their alexithymia but rather are a consequence of the ego's inability to modulate distressing affects. Indeed, in a separate pilot study of newly abstinent alcoholics who were tested both before and after a 3-week period of treatment, Haviland et al. (10) found no significant change in the mean alexithymia score despite a significant drop in the mean depression score as the level of psychological distress subsided. Prospective longitudinal studies are clearly required to further

evaluate the direction of causal relationships among alexithymia, substance abuse, and other associated psychopathology.

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Prevalence of Neuroleptic-Induced Dystonia in Mania and Schizophrenia

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In a prospective study of 41 acutely psychotic patients, neuroleptic-induced dystonic reactions occurred in 62.5% of the manic patients (10 of 16) and 66.7% of the schizophrenic patients (10 of 15), a nonsignificant difference. These findings contradict a recent report suggesting a higher risk for this side effect in mania.

(Am J Psychiatry 1990; 147:1231–1233)

I n a recent retrospective chart study, Nasrallah et al. (1) found the prevalence of acute dystonic reactions associated with neuroleptic therapy to be significantly higher in manic patients (26.1%) than in schizophrenic patients (5.9%). The notion that neuroleptic-induced side effects may vary between these diagnostic categories is not a new one. Other reports (2–4) have indicated that tardive dyskinesia is more common in patients with affective disorders who are treated with neuroleptics than in schizophrenic patients receiving neuroleptics.

In some studies (5) diagnosis was not reported to be a risk factor in neuroleptic-induced acute dystonias, although other variables, such as sex, age, and neuroleptic potency, have been identified. Nasrallah et al. (1) underscored the retrospective nature of their chart review and the need for a prospective replication. We conducted a prospective study of parenteral neuroleptic treatment in acute psychosis and compared the prevalence of acute dystonic reactions in manic and schizophrenic patients.

METHOD

The study was carried out over 3 years on the acute, brief-stay unit of a 138-bed postgraduate teaching hos-

pital and was designed to evaluate clinical and pharmacologic correlates of haloperidol treatment over a 14-day period. The patient sample consisted of acutely psychotic patients between the ages of 18 and 55 who were judged by the emergency room psychiatrist to require hospitalization and parenteral neuroleptic treatment. Patients who had been treated with a depot neuroleptic within the last month or who had taken oral neuroleptics within 5 days of the assessment were excluded. Other exclusion criteria were clinically significant abnormalities in cardiac, renal, or hepatic function, evidence of organic brain disease, acute intoxication, use of anticonvulsant medication, a recent history of alcohol and/or substance abuse, and pregnancy or suspected pregnancy. Informed consent was required for participation in the investigation.

In accordance with reports outlining the safe and efficacious use of neuroleptic therapy in the treatment of acute psychosis (6), intramuscular haloperidol, 10 mg hourly to a maximum of 80 mg, was administered during the first 24 hours. The total amount given during this period was determined by the treating psychiatrist and was based on the clinical goal of sedation or adequate behavioral control to permit socialization on the unit. On day 2, haloperidol was converted to a daily oral dose 1.5 times the total day 1 parenteral dose, in keeping with the routine clinical practice of switching to oral administration as quickly as possible and documented pharmacokinetic differences between these two routes of administration for haloperidol (6). To reduce the dose gradually after the initial pharmacologic intervention, the subjects received 75% of the total day 2 haloperidol dose on days 5 and 6 and 50% of the total day 2 dose on days 7–14.

Nursing staff and/or physicians, blind to the specific purpose of this investigation, documented any acute dystonic reactions that occurred, specifically noting their nature, the exact time of onset, treatment, and response. Acute dystonic reactions were distinguished from tardive dyskinesias by their sudden onset, acute discomfort and distress to the patient, and rapid resolution after the immediate administration of either intramuscular or intravenous benztropine mesylate.

Diagnosis was based on *DSM-III* criteria and required the agreement of two physicians, who were also blind to the specific purpose of this study.

TABLE 1. Characteristics of Manic and Schizophrenic Patients Who Did or Did Not Develop Acute Dystonic Reactions After Intramuscular Administration of Haloperidol

Patient	Age (years)	Sex	Schizophrenic Subtype	Total Intramuscular Haloperidol Dose on Day 1 (mg)	Acute Dystonic Reaction Type	Hours After Initial Dose
Bipolar disorder, manic						
Dystonia						
1	31	M	—	60	Trismus	25.0
2	29	M	—	10	Torticollis	25.5
3	23	F	—	50	Tongue protrusion	26.0
4	37	M	—	50	Trismus, tongue protrusion, oculogyric crisis	48.5
5	23	F	—	30	Retrocollis	36.0
6	22	M	—	70	Torticollis	28.5
7	23	M	—	40	Tongue protrusion	29.0
8	24	F	—	40	Torticollis	23.5
9	24	F	—	40	Torticollis	27.5
10	24	M	—	30	Glossopharyngeal contractions	21.0
No dystonia						
11	30	F	—	20	—	—
12	26	F	—	20	—	—
13	34	M	—	50	—	—
14	41	F	—	40	—	—
15	52	M	—	20	—	—
16	25	F	—	50	—	—
Schizophrenia						
Dystonia						
17	23	M	Undifferentiated	30	Intermittent muscle spasms	27.0
18	32	M	Paranoid	40	Intermittent muscle spasms	31.0
19	31	M	Paranoid	20	Tongue protrusion, trismus	25.5
20	34	F	Paranoid	30	Oculogyric crisis, retrocollis	27.5
21	26	M	Paranoid	20	Tongue protrusion, trismus	1.0
22	27	F	Paranoid	10	Intermittent muscle spasms	28.5
23	31	M	Disorganized	40	Torticollis, trismus	17.5
24	30	M	Paranoid	20	Torticollis	27.5
25	20	M	Undifferentiated	30	Tongue protrusion	18.0
26	35	F	Paranoid	20	Trismus	28.5
No dystonia						
27	36	M	Paranoid	50	—	—
28	21	M	Paranoid	30	—	—
29	36	F	Paranoid	20	—	—
30	31	M	Paranoid	20	—	—
31	31	F	Undifferentiated	60	—	—

To evaluate the factors of diagnosis (mania versus schizophrenia) and sex distribution, Fisher's exact probability was calculated. Student's t tests were used to analyze group differences in age, total parenteral neuroleptic dose, and time of acute dystonic reactions.

RESULTS

A summary of the data is provided in table 1. Of the 41 subjects who participated, 16 met the *DSM-III* criteria for bipolar disorder, manic, and 15 were diagnosed as suffering from schizophrenia. Ten met the criteria for other diagnostic categories (brief reactive psychosis, N=2; schizophreniform disorder, N=3; delusional disorder, N=2; schizoaffective disorder, N=1; organic affective syndrome, N=1; atypical psychosis, N=1). Of the 31 patients with diagnoses of mania

or schizophrenia, 20 (64.5%) experienced acute dystonic reactions. This represented 62.5% of the manic patients (10 of 16) and 66.7% of the schizophrenic patients (10 of 15), a nonsignificant difference (p=1.00, Fisher's exact test).

For the nondystonic group (N=11), there was no significant difference between manic and schizophrenic patients in total amount of parenteral haloperidol received over the first day of treatment (mean±SD=33.3±15.1 versus 36.0±18.2 mg; t=0.27, df=9, p>0.05). However, among the dystonic patients, the manic patients received significantly more parenteral haloperidol than the schizophrenic patients during this same time period (42.0±16.9 versus 26.0±9.7 mg; t=2.60, df=18, p<0.05). Nonsignificant age differences were found between the manic and schizophrenic patients in both the dystonic group (26.0±4.8 versus 28.9±4.8 years; t=1.34, df=18, p>0.05) and

the nondystonic group (34.7±10.3 versus 31.0±6.1 years; t=0.70, df=9, p>0.05). There were also no significant differences in sex distribution between the manic and schizophrenic patients in the dystonic group (four women and six men versus three women and seven men) and the nondystonic group (four women and two men versus two women and three men) (p= 1.00 and 0.78, respectively, Fisher's exact test). Finally, the time of acute dystonic reaction was not significantly different between the manic and schizophrenic patients (29.1±7.9 versus 23.2±9.0 hours after initial dose; t=1.55, df=18, p>0.05).

DISCUSSION

Our results, established in a prospective study, failed to support the findings of Nasrallah et al. (1); almost equal proportions of the manic and schizophrenic patients developed neuroleptic-induced dystonic reactions. Several noteworthy features distinguish this investigation from the study of Nasrallah et al. (1). All of our patients were treated with parenteral haloperidol, whereas their patients received a number of neuroleptics. By using this particular high-potency agent, we were in a sense maximizing the risk for dystonic reactions, particularly as none of these patients was prophylactically given antiparkinsonian medications (7, 8). As this was a prospective study, we were willing to accept patients who met the DSM-III criteria for paranoid schizophrenia, a group excluded in the chart review of Nasrallah et al. (1) because of concerns about diagnostic specificity. Indeed, the majority of our schizophrenic patients were of the paranoid subtype. While there was no significant difference between the neuroleptic doses for the schizophrenic and manic patients in Nasrallah et al.'s study, our manic patients in the dystonic group actually received significantly higher total haloperidol doses than the schizophrenic patients, but they exhibited no higher prevalence of acute dystonic reactions. None of our manic patients was receiving lithium concomitantly. In contrast, all of the manic patients in the report of Nasrallah et al. were taking lithium in addition to neuroleptics, leading Nasrallah and associates to speculate on the possible risk related to the simultaneous intake of lithium. In the

additional variables that we looked at—i.e., gender, age, time of acute dystonia—no significant differences could be found between the manic and schizophrenic patients.

Nasrallah and associates noted that the similarity between acute and tardive dyskinesia symptoms suggests a similar pathophysiologic mechanism in the extrapyramidal system. However, our current understanding of the pathophysiology of neuroleptic-induced dystonic reactions and tardive dyskinesia suggests different underlying mechanisms (9, 10). Therefore, it may be a mistake to expect clinical findings related to these two distinct types of side effects to parallel each other. While there has been evidence of a higher risk for tardive dyskinesia in bipolar than in schizophrenic patients (2–4), the present study fails to support the hypothesis that a similarly higher risk applies to neuroleptic-induced dystonic reactions in patients with the diagnosis of bipolar disorder, manic.

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Positive and Negative Symptoms and Social Competence in Adolescents at Risk for Schizophrenia and Affective Disorder

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The authors compared adolescents at risk for schizophrenia and affective disorder and normal adolescents. The subjects at risk for schizophrenia had significantly poorer social competence, and formal thought disorder was greater in both high-risk groups. There were no group differences in negative symptoms.
(Am J Psychiatry 1990; 147:1234–1236)

The symptoms of schizophrenia are diverse, and there have been numerous attempts to organize this complexity in a meaningful fashion. One well-known attempt was made by Strauss et al. (1), who proposed that positive symptoms, negative symptoms, and disorders of social relationships reflect three separate underlying processes in the development of schizophrenia. The distinction between positive and negative symptoms has become increasingly prominent in research on schizophrenia (2, 3), but the third group of symptoms identified by Strauss et al.—disorders of social relationships—has received only limited attention in these studies. Although poor social functioning has been considered a negative symptom (2), the results of research on genetic influences (4) and sex differences (5) suggest that social functioning and positive and negative symptoms reflect relatively independent underlying processes.

To complement these data, it is important to deter-mine whether these three types of symptoms have different longitudinal trajectories in the developmental course of schizophrenia. Crow (3) suggested that a predominantly positive symptom syndrome often develops into a predominantly negative symptom syndrome, but the developmental unfolding of positive and negative symptoms before the onset of diagnosed schizophrenia has received less attention. In this study we examined high-risk offspring of parents with schizophrenia and affective disorder in order to investigate positive and negative symptoms and social competence before diagnosis of schizophrenia.

METHOD

The New York High-Risk Project was begun in 1971 by Erlenmeyer-Kimling (6). Two independent samples are included in the project; the present study was based on the first of these, ascertained in 1971–1972. From consecutive admissions to psychiatric facilities in the New York area, patients with intact marriages and 7- to 12-year-old children with no evident psychiatric disorder or mental retardation were diagnosed according to the Research Diagnostic Criteria, using information from hospital records and the Schedule for Affective Disorders and Schizophrenia—Lifetime Version. On the basis of comparisons of the major variables examined in the project, the offspring of parents with diagnoses of schizophrenia and schizoaffective, mainly schizophrenic, disorder were combined, as were the offspring of parents with diagnoses of affective disorder and schizoaffective, mainly affective, disorder. An adolescent comparison group was obtained through the cooperation of two large school districts in which the majority of the high-risk subjects lived. Children in this group were 7–12 years of age, from intact homes, and without histories of psychiatric problems or mental retardation. Families in which either parent had had psychiatric hospitalization or treatment or a history of psychiatric problems were excluded from this normal comparison group (C).

The three groups of offspring were assessed at 2- to

TABLE 1. Scores of Adolescents at Risk for Schizophrenia and Affective Disorder and of Normal Adolescents on Measures of Social Competence and Negative and Positive Symptoms

Measure	R^a	Score[b]						Analysis	
		Offspring of Parents With Schizophrenia (N=36)		Offspring of Parents With Affective Disorder (N=34)		Normal Comparison Adolescents (N=83)		F (df=2, 150)	p^d
		Mean[c]	SD	Mean[c]	SD	Mean[c]	SD		
Social competence scale	0.80	$1.55_{x,y}$	0.73	1.19_x	0.61	1.05_y	0.63	7.21	0.001
Affective flattening scale	0.80	0.44	0.52	0.25	0.42	0.35	0.51	1.26	0.29
Poverty of speech rating	0.66	0.61	0.78	0.43	0.72	0.58	1.01	0.44	0.64
Positive formal thought disorder scale	0.73	0.09_x	0.20	0.09_y	0.20	$0.02_{x,y}$	0.07	4.61	0.01
Positive formal thought disorder global rating	0.57	0.21	0.45	0.24_x	0.55	0.05_x	0.21	3.87	0.02

[a]Intraclass correlation coefficient for interrater reliability on the mean ratings.
[b]For all measures, higher scores reflect greater pathology.
[c]Means sharing the same subscript differed significantly at $p<0.05$ in Tukey-Kramer tests.
[d]Conventional significance levels based on one-way analyses of variance. The significance levels based on the multistage Bonferroni procedure were as follows: $p<0.005$ for the social competence scale and $p<0.05$ for the positive formal thought disorder scale. Differences on the remaining measures were not significant.

3-year intervals with a variety of biobehavioral and clinical measures (6). At the third testing round, 30-minute semistructured, videotaped interviews were administered by psychiatrists who were blind to the subjects' group membership. These interviews were rated in separate randomized orders by each of two randomly chosen raters from a group of three advanced clinical psychology graduate students, also blind to the subjects' group membership. They made ratings of 36 offspring of parents with schizophrenia, 34 offspring of parents with affective disorder, and 83 normal comparison offspring. The mean±SD age of the subjects at this testing round was 15.0±1.97 years.

Social competence was assessed on subscales for adolescents from the Premorbid Adjustment Scale (7) that were modified for this study. On the basis of research on negative symptoms (3, 8), four items reflecting affective flattening (unchanging facial expression, poor eye contact, affective nonresponsivity, and lack of vocal inflections) and the poverty of speech rating were selected from the Scale for the Assessment of Negative Symptoms (2) to assess these two symptoms, which are considered the core of the negative syndrome (3). The global rating and the mean score on the positive formal thought disorder subscale of the Scale for the Assessment of Positive Symptoms (N.C. Andreasen, unpublished 1984 manual) were both used to assess this positive symptom. The remaining symptoms from the scale for positive symptoms were not rated because few of the offspring exhibited them by midadolescence.

RESULTS

The interrater reliabilities of the means for the two raters, presented in table 1, were generally satisfactory. As can be seen from the remainder of the table, after

Bonferroni correction there were significant group differences in social competence and in the positive formal thought disorder scale but not in the two negative symptoms nor in the positive thought disorder global rating. In Tukey-Kramer tests, the adolescents at risk for schizophrenia had significantly poorer social competence than the adolescents at risk for affective disorder and the normal comparison adolescents; the adolescents at risk for schizophrenia and affective disorder had significantly higher scores on the positive thought disorder scale than the normal comparison adolescents but did not differ significantly from each other.

There were no significant group differences in age or sex. To examine possible sex differences in the results, two-way analyses of variance were conducted for each of the five measures. No significant interactions of Group by Sex were found. IQ and parental social class were significantly higher in the normal comparison group than in the two high-risk groups, which did not differ significantly. When these two variables were controlled in analyses of covariance, the differences between the high-risk and normal comparison adolescents remained significant, except for the difference in positive thought disorder between the adolescents at risk for schizophrenia and the normal comparison adolescents (however, see reference 9 for a discussion of the limitations of this use of analysis of covariance).

DISCUSSION

Adolescents at risk for schizophrenia had significantly poorer social competence and significantly higher levels of positive formal thought disorder than a comparison group of normal adolescents. But adolescents at risk for affective disorder also had significantly higher levels of positive thought disorder than the

comparison adolescents, suggesting that the positive formal thought disorder which is apparent in these high-risk adolescents is not specific to those at risk for schizophrenia. Only scores on the social competence measure significantly differentiated the two high-risk groups. Not only were the adolescents at risk for schizophrenia significantly poorer in social competence than the normal adolescents—a result that is consistent with a great deal of prior research (10)—they were also significantly poorer in social competence than the adolescents at risk for affective disorder, who did not differ from the normal comparison adolescents. In these data, therefore, deficits in social competence were characteristic of adolescents at risk for schizophrenia but not adolescents at risk for affective disorder. These group differences may reflect vulnerability to later psychopathology in the high-risk adolescents, but they may also be the result of rearing by disturbed parents; thus, it is important to determine whether the results for each of the high-risk groups as a whole remain characteristic of those necessarily fewer adolescents who later develop schizophrenia or affective disorder.

Poorer social competence was significantly associated with higher scores for each of the two negative symptoms we examined—affective flattening and poverty of speech—in all three groups of adolescents (Pearson correlation coefficients ranged from 0.40 to 0.59, all with $p<0.05$). Similarly, in patients with schizophrenia, significant correlations have been reported between poorer premorbid social competence and greater numbers of negative symptoms after the onset of illness (2, 4). Such correlations indicate that these two dimensions of schizophrenic psychopathology are reliably associated. However, the moderate magnitude of these correlations, the results of research on genetic influences (4) and sex differences (5), and the fact that we found significant group differences in social competence but not in negative symptoms suggest that these two dimensions are not interchangeable and must be examined separately in future research.

In our data, the dissimilarity of the patterns of group differences in positive formal thought disorder, negative symptoms, and social competence is consistent with the relative independence of these three dimensions in schizophrenia. Our results therefore provide further support for a multidimensional approach to the development of schizophrenia (1, 3–5). The central hypothesis of this approach is that different symptoms—positive and negative symptoms and social functioning—reflect separate functional processes (1), and it is anticipated that a more complete understanding of schizophrenia will result from the coordinated investigation of the developmental course of these symptoms and their underlying processes.

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Book Forum

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TEXTBOOKS

Symptoms in the Mind: An Introduction to Descriptive Psychopathology, by Andrew Sims. Philadelphia, Baillière Tindall (W.B. Saunders Co.), 1988, 318 pp., $23.95.

It isn't often that a book comes along and fills an important gap in the professional literature, so that one wonders how the profession did without it. *Symptoms in the Mind* is just such a book. This is a clear, in-depth exploration of the phenomenology of the signs and symptoms of mental disorders. The majority of its 23 chapters discuss different aspects of the mental status examination with very palatable rigor.

Chapter one discusses fundamental concepts, including phenomenology, the empathic method of understanding, applying understanding versus explanation to symptoms, primary and secondary symptoms, and the form and content of symptoms. The influence of Jaspers is obvious, and Sims ascribes proper credit to Jaspers and many other underappreciated, mainly European, predecessors. I would place Sims's work between *Clinical Psychopathology* by Frank Fish (1) and Jaspers's *General Psychopathology* (2). Fish's work is admirable for its succinctness and accessibility, and Jaspers's tome excels in its depth and comprehensiveness but can put off the uninitiated.

Further chapters discuss disturbances of consciousness, attention, memory, time sense, and perception, including myriad types of hallucinations and a clear discussion of pseudohallucinations. Disorders of language and speech appropriately get a separate chapter from disorders of thinking process.

Professor Sims, from St. James Hospital in Leeds, is Dean of the Royal College of Psychiatrists. From his British perspective he has been able to go beyond the sometimes constricting approach associated with *DSM-III*. This allows him to discuss neurotic symptoms, which still exist outside of the United States, quite richly, and the same is the case for personality disorders, including the anancastic and the asthenic.

Particularly impressive is chapter seven, "Delusions and Other Erroneous Ideas." It is actually embarrassing that we have so oversimplified this area in our clinical communications. Included in this chapter are discussions of primary and secondary delusions, Jaspers's concept of "un-understandability" and meaningful connections, autochthonous delusions, delusional percepts, delusional atmosphere (mood), delusional memory, and overvalued ideas. Also explained is the correct meaning of the word "paranoid," which in fact is "self-referent" and not limited to persecutory. In chapter 22, "Eliciting the Symptoms of Mental Illness," Sims offers some sage advice on how to sensitively elicit symptom phenomenology. Sims advises that "several short interviews are preferable to a marathon session" and warns the enthusiast not to be "digging for phenomena like a dog at a rabbit hole."

Sims's writing style and the book's organization make it readily digestible. The references are remarkably thorough, and the print is pleasing to the eye. For psychiatrists who

fancy themselves professionally as thoroughbreds and not just journeymen, *Symptoms in the Mind* is essential reading. Full marks to Sims.

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Psychiatric Diagnosis, 4th ed., by Donald W. Goodwin, M.D., and Samuel B. Guze, M.D. New York, Oxford University Press, 1989, 314 pp., $29.95; $16.95 (paper).

The fourth edition of *Psychiatric Diagnosis* has arrived, right on schedule. Every 5 years since its initial publication in 1974, this book—now a classic in psychiatric nosology—has been revised to reflect progress in our understanding of mental disorders.

The new edition makes some concessions to be modern, for example by including *DSM-III-R* criteria and wrapping the paperback version inside a day-glo fuchsia and metallic silver cover, yet remains remarkably faithful to the tried and true formula of the original. Of the 12 chapters in the first edition, 11 remain, albeit some with new terminology: "Affective Disorders," "Schizophrenic Disorders," "Panic Disorder (Anxiety Neurosis)," "Hysteria (Somatization Disorder)," "Obsessive Compulsive Disorder," "Phobic Disorders," "Alcoholism," "Drug Dependence," "Sociopathy (Antisocial Personality)," "Brain Syndrome," and "Anorexia Nervosa." Only the original chapter on sexual problems has been dropped from this edition, for unknown reasons, and a chapter entitled "The Psychiatric Examination" has been added. The disorders discussed are those which Drs. Goodwin and Guze believe "have been sufficiently studied to be useful" (p. xi).

The disorder-focused chapters continue to be divided into sections on definition, historical background, epidemiology, clinical picture, natural history, complications, family studies, differential diagnosis, and clinical management. Further emphasizing the empirical basis of their approach, the authors have added even more references to the scientific literature, now tripling the number included in the first edition. Expanded treatment sections, the addition of clinical vignettes, and inclusion of new findings on biological aspects of mental disorders also characterize the evolution of the book.

In considering what could be said about a book that has already been reviewed dozens of times, I reviewed a number of the reviews. Many of these reviews said that *Psychiatric Diagnosis* might be most useful for medical students, resi-

dents, and other novices, implying that it offers less to the seasoned professional. I doubt that there is a single mental health professional who would not learn a great deal by reading this information-packed book.

If some clinicians fail to embrace *Psychiatric Diagnosis*, it may be because of the book's relatively limited coverage of psychiatric disorders. The authors stress the solid evidence supporting the validity of the discussed diagnoses, but a large proportion of patients seeking and receiving psychiatric treatment today may not have one of these well-validated disorders. Although researchers may be comfortable with assigning patients to an "undiagnosed psychiatric illness" category, clinicians in practice may be more reluctant to do so. The many categories classified and described in *DSM-III-R* at least allow clinicians to organize their thinking about the clinical phenomenology of their patients, although we all should recognize that many *DSM-III-R* categories possess only "face validity."

On reading this book, one might also wonder why, after more than 15 years, the only substantive change in the number of diagnostic categories that have been validated—and therefore included in this edition of *Psychiatric Diagnosis*—is the loss of one category. Certainly diagnostic criteria of the type originated by the Washington University group and built on in the Research Diagnostic Criteria and *DSM-III* have stimulated research on the antecedent, concurrent, and predictive validity of defined categories. Perhaps no other mental disorders will meet strict criteria for validity or perhaps it is too early to have fully reaped the benefits of the so-called neo-Kraepelinean revolution in psychiatry.

Another possibility seems intriguing. The approach to validating psychiatric diagnoses proposed by Robins and Guze in 1970, which has become gospel, suggests that a valid diagnostic entity is familial, indicates a homogeneous prognosis, and, ultimately, reveals an underlying, consistent, and coherent pathophysiology and etiology. Recent research seeking to validate the *DSM-III* diagnosis of schizophrenia has yielded paradoxical results: although the narrow *DSM-III* definition has been shown (with only one notable exception) to predict a uniformly poor course and outcome, it is no better than much broader definitions in identifying persons with a familial, possibly genetic, illness. Possibly, a severe form of the disorder is best for prognostic purposes and a much milder form for identifying persons exposed to certain risk factors. If so, then the expectation that external validators converge on a single definition of a disorder may be unrealistic or even misleading. Furthermore, recent interest in the phenomenon of "comorbidity," or syndromal complexity, in psychiatric illness suggests that all useful psychiatric diagnoses may not represent completely separate and discrete disorders but, rather, aspects of clinical heterogeneity that may have important etiological, prognostic, and treatment implications.

Goodwin and Guze, in the preface to their fourth edition, lay claim to having anticipated the revolution in psychiatry in the last decade and a half, which has resulted in unprecedented interest in reliable diagnosis and rigorous empirical study. No one can dispute their claim. *Psychiatric Diagnosis* is a bench mark in the field. It will be interesting to see what the next 5 years bring.

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Future Directions for Psychiatry, *edited by John A. Talbott, M.D. Washington, D.C., American Psychiatric Association, 1989, 251 pp., $22.00 (paper).*

The profession of medicine, including its specialties, is in a period of rapid change. Some compare it with what we have seen in the political situation in Eastern Europe. The pace has not been so fast in psychiatry, although slower changes can have far-reaching effects for our specialty. Research findings have advanced our basic and applied knowledge. Patient care systems present challenges to us in many areas. Education throughout the professional life of the psychiatrist is a fact, and with specialty recertification and the recognition of subspecialties in our field we have opportunities to render the best possible service to our patients, students, colleagues, and administrative bodies, while having accountability and responsibility for our decisions. It is understandable, therefore, that our leaders are sensitive and responsive to the challenges and opportunities that face us as we approach the year 2000.

The present volume results from the planning for and implementation of a conference on the Future of Psychiatry that was held on November 30 and December 1, 1987. *Future Directions for Psychiatry,* filled with stimulating ideas, synthesizes what emerged from these meetings and the subsequent considerations given to the ideas when they were further processed after the conference. Dr. Talbott, the convener of the conference and editor of this excellent monograph, notes that Harold Visotsky first raised the idea of a conference with him in 1983. The explosion of basic and clinical information, technology, and economics-financing was rapidly gaining momentum, and a national meeting of leaders from many areas of psychiatry could be very useful. The APA Board of Trustees approved the plan, and it became operational.

This monograph opens with a comprehensive but brief foreword by Herbert Pardes, APA President for 1989–1990. Dr. Pardes succinctly lists the strengths and problems of modern psychiatry. The details of his outline are addressed in the 14 chapters of the volume itself. There are three appendixes, one of which is "Metapapers Prepared for the APA Group to Plan a Conference and Related Activities on the Future of Psychiatry." These 14 preliminary essays are excellent—written clearly, defining the issues, and, as preconference background documents, alerting the actual conference participants to the agendas of the meeting.

In his introduction, Dr. Talbott clearly delineates the goals, purposes, and questions that confronted the conference group. The honing down of the questions yielded five questions that five work groups of five experts each were asked to answer. These questions were 1) What will be the *future of the science* of psychiatry? 2) What will be the *future of clinical psychiatry*? 3) What are the *economic* strategies to realize these futures? 4) What are the *educational* strategies to realize them? and 5) What are the *organizational* strategies? (p. xxi).

As the reader will note, much excellent work went into thinking through the issues and addressing strategies and plans even before the conference took place. In the first chapter, "Executive Summary: Major Recommendations," the essence of the conclusions of the conference are succinctly presented. The following chapters, some with multiple authors, go into greater detail in addressing the topics in depth and then providing a list of references for any reader who wishes more detail. In the last chapter Dr. Talbott summarizes the consensus and differences of the conferees.

We are already confronting new issues today, but most are

related to themes addressed or hinted at in this excellent report. This document is clear, direct, succinct, and pertinent. It can be read profitably by psychiatric leaders, teachers, researchers, administrators, and students at all levels as well as community support group members and government and foundation officials.

This is a job very well done, successfully completed. Now that we see the challenges and the options, what do we do with them?

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Psychiatric Interviewing: A Primer, 2nd ed., *by Robert L. Leon. New York, Elsevier, 1989, 193 pp., $23.50.*

The ability to effectively communicate with patients remains the cornerstone of clinical medicine and psychiatry. The ideal model of the physician-patient relationship is represented by the supportive and attentive physician who listens to a patient's complaints, assesses the amount of emotional support required, and delivers an appropriate dose of advice and reassurance with whatever medical therapy is prescribed. The current state of medical practice, however, has threatened this ideal. Aggressive consumer advocacy, the specter of malpractice, increased government regulations, managed health care systems, and a greater emphasis on biotechnology have all at least partially diluted the personal aspects of the physician-patient relationship, which is so dependent on good communication. In this context, any text developed to assist the ability of medical students to communicate with and psychologically support their patients is welcome and needed.

In this second edition of *Psychiatric Interviewing: A Primer* the author renews his effort to present a model of psychiatric interviewing designed to facilitate effective communication between physician and patient. The text has good intentions and basically sound content but tends to suffer from the absence of a comprehensive structural model for patient interviewing that would have given the overall approach more organization and internal consistency. Rather than setting out such a model from the first and developing essential components of the psychiatric interview in sequential manner, the text tends to meander in and out of discussions of basic interviewing concepts, psychiatric assessment, and principles of psychodynamic psychotherapy. Therefore, it is not entirely clear whether the goal of the text is to be a guide to basic medical versus psychiatric interviewing skills; in reality the book appears to be a mixture of the two approaches.

Although most of the text is written by Dr. Leon, a few chapters (on human sexuality, the mental status examination, and cultural influences on interviewing) were delegated to invited contributors, which tends to interrupt the consistency of the text's style and approach. The book could have benefited from an expanded section on the mental status examination, which is given only 12 pages. The text does not pretend to be a guide to comprehensive psychiatric assessment, but the lack of a discussion of psychiatric differential diagnosis makes the chapter on the mental status examination—and to some extent the entire text—incomplete.

Other criticisms should be noted—for a second edition the references are somewhat dated. For example, a more updated discussion of recent primary care research demonstrating the relationship between physician-patient communica-

tion and treatment outcome (such as compliance) and patient satisfaction would have improved the author's case for the importance of developing good communication skills in the medical setting. Certain areas of special importance would have benefited from much more attention—such as interviewing paranoid, suicidal, hypochondriacal, and sexually provocative patients. In addition, the entire text could have benefited from more case examples illustrating model positive interactions between physicians and patients.

Although the essential content of this small introductory text is generally valid, its lack of structure and its lack of a more in-depth discussion of problematic types of patients will to some extent restrict its usefulness as a guide to patient interviewing. For course directors interested in texts that provide more structure and depth, I recommend Shawn Shea's lengthy, detailed, but comprehensive *Psychiatric Interviewing: The Art of Understanding* (1) as an alternative. Another more general text to consider for medical interviewing would be David Reiser and Andrea Schroder's *Patient Interviewing: The Human Dimension* (2). Nevertheless, *Psychiatric Interviewing: A Primer* could serve as a general guide for discussing introductory aspects of patient interviewing with medical students if used in conjunction with careful clinical supervision and supplemental reading, particularly in respect to the mental status examination and psychiatric differential diagnosis.

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SOMATIC THERAPIES

Physical Treatments in Psychiatry, *by L.G. Kiloh, J.S. Smith, and G.F. Johnson. Cambridge, Mass., Blackwell Scientific Publications, 1988, 478 pp., £49.50.*

This is an excellent new textbook on somatic treatments, written for clinicians and students by an Australian team of clinician-authors. It describes clinical psychopharmacology, ECT, and psychosurgery in detail. Leslie Kiloh is the author of the often-quoted 1961 description of pseudodementia as well as numerous reports on psychosurgery and psychopharmacology. His coauthors have done extensive research in psychopharmacology and psychosurgery.

The historical introduction gives a good description of the empiricism that dominated psychiatric research in the past century, including the development of malaria therapy of dementia paralytica by Wagner-Jauregg in 1917, convulsive therapy by Meduna in 1934, and leukotomy by Moniz in 1935. More recent developments are described in introductions to the appropriate chapters.

The section on psychopharmacology systematically describes the pharmacology, pharmacokinetics, preparations and doses, indications, use, adverse effects, contraindications and precautions, and drug interactions for antipsychotic, antimanic, antidepressant, and anxiolytic substances. The description of lithium is particularly well written and reflects an

experience that the authors share enthusiastically with the readers. The uses of lithium in nonmanic states—depression, aggression, alcoholism, and schizoaffective conditions—are of special interest. Overall, the chapter is a useful and readable summary of modern pharmacotherapy.

The description of ECT is excellent and compares favorably with other texts. Descriptions of the early years of the ECT era, sham treatments, and self-reports of professionals who underwent courses of ECT are delightfully written. The technical aspects of the treatment are useful, although the preference for unilateral ECT is inconsistent with recent recommendations of the Royal College of Psychiatrists, which encourage the use of bilateral electrode placements. Benzodiazepines are recommended to allay patient anxiety before treatment, but there have been recent injunctions against their use because they raise seizure thresholds, interfere with the adequacy of the induced seizure, and impair the efficacy of ECT.

The authors encourage the use of brief-pulse ECT modified with anesthesia and muscle relaxation, but they also recognize reality when they write, "These recommendations are an attempt to achieve the ideal. For economic and other reasons, particularly in third world countries, the ideal may be unattainable. If so, ECT should not be withheld if there is convincing evidence that the treatment is indicated. It is far better if there is no alternative to use unmodified bilateral ECT with sinusoidal currents than to leave the patient to suffer." The same may be said, unfortunately, about our public (state, municipal, and Veterans Administration) hospitals that do not provide ECT for their patients.

The large chapter on psychosurgery is well written and provides the best review of the subject in modern texts. The enthusiasm of its early advocates, its widespread overuse, and the legal injunctions that brought its use to an abrupt end are well described. The authors seem reluctant to accept this opinion and argue that there still remain patients with severe agitated depression and obsessive-compulsive states, unresponsive to other therapies, for whom selective brain ablations may be of benefit. Their opinion reflects that of the U.S. National Commission that reviewed the psychosurgery data and concluded in 1977 that further trials in research settings were warranted. Psychosurgical procedures may well have been discarded prematurely.

Among the dubious therapies noted in this book are Lippold's polarization, electrosleep, prolonged narcosis, and megavitamin treatments. These are not encouraged, and one is awed by the ingenuity of our predecessors when faced with caring for the severe mentally ill without our modern pharmacological agents. It is unclear why a description of insulin coma is omitted; it was a widely used treatment, probably more so than those described in the sections on psychosurgery and the dubious therapies.

The chapter on legal considerations is focused mainly on the psychosurgery debates and complements that section. There is an extensive reference list (92 pages) with about 1,600 citations. There is also a very good index.

This text on somatic treatments in psychiatry reflects the authors' clinical experience and interests. It is in the tradition of Sargant and Slater in Great Britain, Kalinowsky and Hoch in the United States, Delay in France, von Braunmühl in Germany, and Roubicek in Czechoslovakia. It is excellent in the sections on ECT and psychosurgery, useful in psychopharmacology (especially regarding lithium), and of archival interest in the remainder. Descriptions of the mode of action of these therapies are poor. The text is well written and well documented; the authors use many personal pronouns, and

the chapters read easily. This text is recommended highly for practicing psychiatrists and residents and should complement modern psychiatric libraries as a clinical sourcebook in its sections on lithium, ECT, and psychosurgery.

MAX FINK, M.D.
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Drug Treatment in Psychiatry, 4th ed., *by Trevor Silverstone, M.A., D.M., F.R.C.P., F.R.C.Psych., and Paul Turner, M.D., B.Sc., F.R.C.P. New York, Routledge, 1988, 272 pp., $29.95 (paper).*

Professors Silverstone and Turner have updated their popular psychopharmacology primer *Drug Treatment in Psychiatry.* It is one of the few introductory texts that integrate current scientific knowledge and clinical practice. This fourth edition reflects the tremendous changes in the understanding of drug action and biochemistry of psychiatric disorders since the first edition was published in 1974. This latest edition confirms again that the authors are experienced clinicians and pharmacologists. The Clinical Applications section of the book is the strongest and is the primary reason that clinicians will benefit from this book. The chapters on the treatment of affective disorders, anxiety, sleep disturbance, and disorders of appetite are particularly strong. More new antipsychotic and antidepressant agents have become available in Great Britain than in the United States since the third edition of this book appeared in 1982; I hope that some of these will become available here. This book gives us a peek into the prescribing practices of our British colleagues.

The first section, General Principles, provides not only a short historical introduction but also chapters on the pharmacology of CNS transmission, factors affecting the action of psychotropic drugs, some behavioral pharmacology studies as they pertain to the drugs we use, and relevant social and psychological aspects of drug treatment.

There are some minor shortcomings. *DSM-III* diagnoses are used except for schizophrenia. This may be because of the European disagreements about two criteria: the 6-month duration of illness requirement and the upper age limit of 45 years for the onset of schizophrenia. The age at onset criterion has been dropped from *DSM-III-R,* and the 6-month duration of schizophrenic symptoms requirement will be changed in *DSM-IV,* in time for the fifth edition of *Drug Treatment in Psychiatry.* Overlooking this, I found the sections on diagnoses otherwise useful for U.S. readers. The discussion of pharmacokinetics and pharmacodynamics could have been more extensive, and I believe that the discussion of pupillometry in psychopharmacology would not be missed. The use of blood levels of chlorpromazine, which has variable active and inactive metabolites, should be deemphasized, and those of haloperidol, which has only one major metabolite, might have more practical use. In the discussion of sexual deviance, one dopamine receptor blocking agent is singled out as having effects on libido, but in reality all antipsychotics can have such side effects. The chapter on anxiety does not include a discussion of the γ-aminobutyric acid-benzodiazepine chloride ion channel complex and its role in anxiety, alcoholism, and their treatments. That meprobamate is still listed for the treatment of anxiety without any caveats seems to be an oversight. These observations are minor distractions in an otherwise carefully rewritten text.

I found this up-to-date overview of current clinical practice, paired with the needed theoretical background, a plea-

sure to read. The references at the end of each chapter give the reader an opportunity for more in-depth study. It will help the general psychiatrist who wants to be updated, the family practitioner, the medical student in training, the medical or psychiatric resident, and any psychologist who treats patients who are taking medication.

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Pharmacotherapy and Mental Retardation, *by Kenneth D. Gadow, Ph.D., and Alan D. Poling, Ph.D. Boston, College-Hill (Little, Brown and Co.), 1988, 343 pp., $24.50 (paper).*

This book begins with a superb preface by Dr. Robert Sovner that clearly illustrates the need for a book of this type. He presents the key issues marking psychopharmacology for retarded persons who are also mentally ill as a unique area of clinical psychiatry. The authors' introduction reviews the format and objectives of their book, and their first chapter presents a succinct overview of the nature of mental retardation from a variety of modern viewpoints. The remaining seven chapters are fine surveys of both the basic and applied dimensions of key psychopharmacological agents currently used to treat the mentally retarded who are mentally ill. The neuroleptics, the agents for the affective disorders, antianxiety medications, sedatives, anticonvulsants, and the stimulants are all excellently reviewed, as well as the many different additional agents used to treat this complex clinical disorder (e.g., the β-blockers, fenfluramine, and naloxone). The presentation of this excellent information is organized in a rather atypical fashion, however. For example, a separate section covering the antidepressants would have been clearer than their inclusion in a single chapter entitled "Other Medications." Nevertheless, the major mechanisms, efficacy, and side effects of these pharmacotherapeutic agents are clearly noted. Separate chapters on basic pharmacology and research methods round out the major focus, and helpful appendixes include a side effects checklist, a tardive dyskinesia identification system, and recent Accreditation Council guidelines regarding the use of pharmacotherapy for the mentally retarded. Finally, the diagrams inside the front and back covers conveniently classify the psychopharmacological agents reviewed within the book.

Gadow and Poling have clearly met their objectives in this book, which can be used by a wide variety of colleagues who work with and for those mentally handicapped citizens whose lives have been complicated by mental illness. Mental health professionals, enlightened parents of retarded patients, and human service administrators are but a few of the types of readers who can and will profit greatly from this book. The superb readability of *Pharmacotherapy and Mental Retardation* is certainly one of its many strengths.

Finally, the topical area of modern psychopharmacology for the retarded citizen, in view of the recent gray cloud that has descended on it secondary to the specious studies of Stephen E. Breuning, is greatly in need of a modern review. This book represents a great step forward toward removing that gray cloud, and I recommend it highly.

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Psychopharmacology: An Introduction, 2nd ed., *by René Spiegel. New York, John Wiley & Sons, 1989, 239 pp., $41.95.*

The stated goal of this book is "to provide a review of psychopharmaceuticals in nontechnical language for psychologists, psychiatrists, and members of other professions dealing with patients who take these drugs." The author, who is with the Sandoz Corporation in Switzerland, asks for hard criticism in his preface. Here it is: this book falls far short of its stated goals and is not likely to be of use to most clinicians whether they are medically trained or not.

To begin, the book is organized in a rather peculiar fashion. There is an overview chapter defining psychotropic drugs but in a very superficial manner. Only seven pages are devoted to neuroleptics, and information regarding their use and their side effects is jumbled together. As an example, tardive dyskinesia is mentioned before any side effects are even defined or described. Technical terms abound, such as "myorelaxant," despite the stated intentions of the author. Sedation is not mentioned in the discussion of the side effects of neuroleptics. Similar problems plague the antidepressant section, which is only five pages long and includes a somewhat idiosyncratic definition of clinical depression. From the very first chapter, therefore, the reader wonders about the purpose of this book and the audience for whom it was intended.

The second chapter is an interesting history of the discovery of psychotropic drugs, including neuroleptics, antidepressants, and benzodiazepines. Although this information is available elsewhere, one finds here the perspective of a drug company on the development of drugs and the occasional serendipitous observations of their psychotropic effects.

The remainder of the book, although nominally dealing with the effect of drugs on neurotransmission, memory, and neurophysiological functioning, actually illustrates the development and testing of new psychotropic drugs in the pharmaceutical industry. How psychotropic drugs work in the brain, especially their effect on EEG function, and the relationship of these observations to further drug testing are discussed in detail. Testing of drugs in normal human subjects and the methods used for evaluating drugs are reviewed somewhat superficially. As an illustration of the development of new drugs, substances for the treatment of memory disorders are described in some further detail.

In general, therefore, this volume on psychopharmacology, unlike others that are currently available, presents the pharmaceutical industry's perspective on the history of the development of new drugs and the techniques for such development. The actual information on psychotropic drugs and their mechanisms of action, clinical uses, and toxicity is exceedingly skimpy; therefore, this volume will be of little use to most practicing clinicians. It may be of interest to psychopharmacology researchers with a special inclination toward drug development.

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Practical Clinical Psychopharmacology, 3rd ed., *by William S. Appleton. Baltimore, Williams & Wilkins, 1988, 199 pp., $27.95.*

In this short spiral-bound handbook the author presents a concise overview of three major areas: 1) the use of antipsy-

chotics, primarily in the context of schizophrenia, 2) the treatment of mood disorders with heterocyclic agents, monoamine oxidase inhibitors, and ECT, and 3) the treatment of anxiety disorders with antianxiety agents. There is in addition a brief chapter outlining the emergency medical treatment of drug overdoses.

Each of the three major sections reviews the diagnoses of the relevant conditions, presenting and supplementing *DSM-III-R*, provides useful advice about what issues to explore before starting to administer medications (i.e., pretreatment factors such as orthostasis that might be later interpreted as drug side effects), and then offers an overview of the relevant agent's basic pharmacology, efficacy, and side effects. These areas are dealt with in a comprehensive and comprehensible fashion. The descriptions of clinical conditions and the specific agents make the volume not just a brief textbook of psychopharmacology but what it is intended to be, a practical guide to the use of psychopharmacological agents in psychiatry.

Of course, there is room to quibble with some of the book's specifics. For example, it is suggested that "it is possible to win cooperation in drug taking at least 99% of the time" in prescribing antipsychotics. Possibly patients in Boston are more compliant than those in Chicago. There is as well a more general criticism that probably is the flip side of the book's sensible, orderly, and nontheoretical method of exposition. Presenting a description of a specific illness and then of a group of drugs used in its management tends to reify drugs as being specific to particular illnesses, for example, heterocyclic antidepressants for depression. Actually what unites this group of drugs and links them to depression is some common biochemical mechanism that is probably just as clinically relevant to panic disorder, obsessive-compulsive disorder, and bulimia. Thus, the book is weakest in areas in which a drug is used outside the logic imposed by the arrangement of the chapters. For example, there is only the briefest discussion of the use of antipsychotics in the treatment of psychotic depression and little on the use of lithium, propranolol, or carbamazepine in the treatment of aggression.

It is possible that a slightly larger book, possibly with fewer tables providing more information than strictly necessary (i.e., a score card for the performance of each antipsychotic relative to placebo or the individual outcomes of 35 double-blind maintenance studies of antipsychotics), with greater mention of "atypical" uses of psychotropics, and with brief chapters on areas of special interest such as child psychopharmacology, geriatric psychopharmacology, and the psychopharmacology of aggression and personality disorders, might make this otherwise useful little text even better.

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PSYCHOANALYSIS

Shame: The Underside of Narcissism, by Andrew P. Morrison. Hillsdale, N.J., Analytic Press, 1989, 197 pp., $27.50.

Since the publication in 1971 of pioneering works by Helen Block Lewis (1) and Heinz Kohut (2), there has been an upsurge of interest in shame. This appreciation of shame is not a new discovery but a rediscovery in psychoanalytic circles and without. Social thinkers as diverse as Charles Darwin, William McDougall, William James, and Friedrich Nietzsche all put great emphasis on shame. With the ascendancy of attention to role theory in the works of John Dewey and George Herbert Mead, appreciation of the significance of shame diminished and fell into virtual oblivion for decades. The appreciation of the role of shame was only partially revived by the monumental work of Sylvan Tomkins (3) and Erving Goffman (4).

There has been a similar pattern in the evolution of psychoanalysis. In his earliest psychological writings discussing the patient's defense against awareness of ideas that were incompatible with the patient's acceptable idea or view of self (5), Freud emphasized shame as the central painful affect that was defended against in retention hysteria, the earliest paradigm for (posttraumatic) psychopathological phenomena. Somehow, however, attention to shame in psychoanalytic thought went underground, especially with unfolding theoretical emphasis on transgression, aggression, unconscious fantasy, and consequent guilt, which tended to replace the model of retention hysteria as the paradigm of psychopathology. Despite Freud's groundbreaking paper "On Narcissism" (6), which approached shame in the context of the ego ideal, it was guilt and anxiety that evolved as the preeminent affective regulators of the psyche in Freud's later work and in that of both the object relations theorists and the ego psychologists who followed him. The reasons for Freud's neglect of shame are complex and probably include political considerations—particularly Freud's antipathy to Alfred Adler's notion of the inferiority complex.

Difficulty conceptualizing the nature of human interactions in such a way that shame rather than guilt or anxiety is the major regulator signalling danger to human bondings may also have contributed to the lack of serious attention to shame. Many therapists have difficulty in acknowledging both the shame that is inherent in the role of patient and the shaming that often is part of the role of interpreter. Despite the contributions of Piers, Singer, and later Erik Erikson, it was only with the publication in 1971 of Helen Block Lewis's *Shame and Guilt in Neurosis* (1) and Heinz Kohut's *Analysis of the Self* (2) that shame became acknowledged as central and the study of shame and of narcissism began in earnest (7).

The current emphasis on shame should not be thought of simply as the ascendancy of another in-vogue affect—just as Heinz Kohut's term "selfobject" is not just another type of relationship. Both terms reflect an expanded vision of the flux of human relatedness and the nature of selfhood, personality cohesion, self-consciousness, and self-esteem and the dependency of these on the immediate social surround. These concepts harken back to the master-slave dialectic of G.W.F. Hegel, and in this century to the work of Jean-Paul Sartre. They signal a major expansion of our conception of selfhood and of the role of affects in the relation of the self to the inner or external other who confers self-esteem, self-consciousness, and selfhood as well as ideals and aspirations for every one of us, not just for those with narcissistic personality disorders. It is this vastly expanded view of the human lot which places shame as the master regulator—the affect signalling danger of significant bondings of the self to others.

It is in the light of this newly acknowledged expansion of the complexity of social relationships as it has unfolded in psychoanalytic thinking since the early 1970s that Andrew Morrison's *Shame* should be viewed. The author, a serious contributor to the literature on both narcissism and shame, offers a unique and nuanced appreciation of the significance

of our late-coming appreciation of shame for a body of psychoanalytic theory that has tended to neglect it or to relegate it to minor status behind anxiety and guilt.

The book is divided into two parts: a detailed consideration of the evolution of psychoanalytic thinking about structure and affect (i.e., about the ego ideal and about shame) followed by a clinical section emphasizing clinical predicaments and the role of shame in these predicaments. Morrison begins by raising questions that place the reader squarely in the center of the psychoanalytic predicament concerning shame. He asks, Is shame to be viewed as a defense against exhibitionism or is it best understood as an affect? Can shame be fully understood within the context of conflict defense psychology or must a broader psychology of the self and its deficits be invoked? Can shame arise in isolation? What is the relationship of shame to guilt? Is shame a manifestation of passivity-dependency and therefore femininity, or does this formulation reflect an outmoded notion of femininity? What is the relationship of shame to anger, rage, contempt, envy, vulnerability, communications, and humiliation? Finally, what is the explicit relationship of shame to narcissism?

Morrison proceeds to a review of the literature on shame that is as thorough and unbiased as any that I have seen on this complex subject. From the standpoint of mainstream psychoanalysis, he lays particular stress on the aspects of the superego concerned with shame, that is to say, the ego ideal and the ideal self. From the point of view of self psychology, he understands the vicissitudes of narcissism and their relation to shame.

Part two of the book begins with a study of shame-related phenomena such as anger and rage, contempt, envy, depression, and humiliation. Discussion of these as phenomena emanating from shame is long overdue. There is a fine chapter on shame and defense that considers shame from the point of view of a reaction formation (i.e., from the sense of shame as a defense) and also takes up the topic of defenses against shame. In subsequent chapters, Morrison distinguishes shame that is part of specifically narcissistic pathology (pathology dominated by fragmentation and need) from shame in the neuroses (shame in predicaments centered around conflicted desire). Morrison pays some well-needed attention to the relation of shame to suicide—still largely neglected in the literature on suicide. There is a chapter on shame and manic-depressive psychosis and an epilogue that sums up Morrison's views and returns to his original questions.

Excellent though this book is, there are a few shortcomings with which I would take issue. I found Morrison's discussion of personality incohesion a bit too confined to borderline phenomena. He seems to overlook the relation of shame to dissociative phenomena. At times, he seems to come close to equating shame with passivity and femininity, an equation that would tend to restrict shame to a particular type of conflict rather than seeing it as fundamental to all human relationships, male or female, pathological or otherwise. Readers familiar with the work of Erving Goffman (4) will be somewhat disappointed that Goffman's fundamental insights into shame as embarrassment that may arise out of lack of deference for the social order are not mentioned. The chapter on manic-depressive psychosis seemed to me the weakest in the book, depending as it does on formulations of a very flawed study done in the 1950s by Mabel Blake Cohen and her colleagues.

These objections notwithstanding, this is a splendid book, full of first-rate scholarship, clinical wisdom, and a fine synthesis that locates shame at the center of narcissistic phenom-

ena in a very wide range of psychopathological predicaments where it is usually overlooked. Part one should be considered a must for every psychoanalytic educator and serious student of the evolution of psychoanalytic theories of affect, superego, and narcissism. Part two, despite some of the flaws mentioned, presents an excellent coverage of the spectrum of shame-related phenomena in narcissistic disorders and other phenomena. Morrison has achieved a first-rate synthesis of mainstream psychoanalytic and self psychological thought. The book is highly recommended to all serious students of dynamic psychopathology and treatment.

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MELVIN R. LANSKY, M.D.
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Countertransference Triumphs and Catastrophes, by Peter L. Giovacchini, M.D. Northvale, N.J., Jason Aronson, 1989, 346 pp., $35.00.

Non licet omnibus adire Corinthum.

—Horace (Epistles)

I have been learning from Dr. Peter Giovacchini for 35 years and I continue to learn from him. His new book is unusually frank in its presentation of vignettes from his apparently very dramatic private practice. It is clearly written and pleasant to read. In one vignette he tells of referring a patient to a younger colleague, who felt very frustrated by her because her main activity in therapy was to sit with her legs crossed and blow cigarette smoke in his face. "At first," Giovacchini tells us, "he became angry and had a desire to hit her. Later he felt strong sexual urges that he just managed to control. Because of these countertransference feelings, he terminated the treatment" (p. 189). Apparently it never occurred to this psychiatrist to discuss with the patient her blowing cigarette smoke in his face and sitting with her legs crossed and to deal with that directly rather than terminating the treatment or struggling with strong internal passions of rage and sexuality.

On the whole, the anecdotes are provocative and exciting; where the book weakens at times is in some of the theoretical discussion, such as the description of Racker's views on countertransference (p. 19) and Giovacchini's "two categories" of psychopathology—character disorders and "those who have fairly intact characters but, in the tradition of the psychoneuroses, also have intrapsychic conflict" (p. 92), all

of which requires a much more extended discussion and explanation, since these are quite controversial and difficult concepts.

The distinction between psychotherapy and psychoanalysis is blurred from the beginning, and the author uses the terms "analyst" and "therapist" interchangeably. The first sentence of the first chapter tells us that "clinicians practicing psychoanalysis—or what has been called psychoanalytically oriented psychotherapy—are becoming increasingly aware that treatment success or failure is a complex issue that stresses the irrational parts of both the therapist's and the patient's personalities" (p. 1). In fact, some hostility to traditional psychoanalysts seems implied in Giovacchini's descriptions of certain analysts who are utterly devoid of common sense. For example, we are told of an analyst who "responded to a patient's insistence that he remove from his wall a painting that she considered ugly. After he had removed the offending painting, she wanted him to hang a picture that she had painted in that same spot. With great reluctance he accepted her painting and hung it. He believed that if he did not, he would lose the patient. The analyst was uneasy about this arrangement, and he did not even like the picture" (pp. 105–106). Another analyst, who presented material during a workshop at which Giovacchini was the co-chairman, "casually mentioned that the patient had defecated on the couch" (p. 142). When Giovacchini asked about this, the analyst was "somewhat surprised at our apparent lack of understanding and explained that he viewed the patient's excretory behavior as representing progress" (p. 142). There is a hint of some sort of countertransference Giovacchini may have to the traditional psychoanalytic movement in what I found to be the most startling sentence in the book: "During my days as a candidate at the Chicago Institute for Psychoanalysis, I never once heard a mention of Winnicott or Melanie Klein or any of her followers" (p. 18).

Beginners should be warned that Giovacchini writes from a thoroughly Kleinian orientation, influenced by Little and Searles. Although it does not often happen, sometimes he goes off the Kleinian deep end. For example, we are asked to believe that a patient "had succeeded in getting me to absorb the emptiness and nonexistence that he felt and that he so vigorously defended himself against. He could resort to the defense of reaction formation as he projected his vulnerability into me" (p. 53). In one instance we are told that a patient was afraid "that some omnipotent power would get out of control, and this was manifested in the transference by her fear of destroying me. She was also afraid that I would attack and devour her. These fears were the outcome of the greed and envy she had projected into me" (p. 269).

This book has some pitfalls for beginners, who may use it to justify irresponsible and irrational behavior and interpretations in the therapeutic process. Giovacchini relates at least two instances (p. 79 and p. 132) when he entirely lost his temper with a patient. This does happen even with the most experienced analysts, but it is not made clear that when it happens the matter should be carefully investigated by self-analysis, and if it happens with any frequency, there is something wrong with the therapist. Giovacchini is a very experienced clinician who can look on his loss of temper and some other countertransference-based behavior with a certain equanimity, whereas a beginner reading this book may conclude that he or she too is permitted "to go to Corinth." Corinth was the Paris of its day, but its pleasures were too costly for many people. Beginning therapists who give free vent to countertransference acting out may well find their practice and their personal lives in a shambles.

In a way, the book might be of greater appeal to experienced psychotherapists because of the provocative nature of some of the views expressed. There are several discussions of the concept of "the impassive, neutral analyst" (p. 2) that show Giovacchini at his best. He distinguishes between Anna Freud's notion of neutrality as representing the maintenance of an equal distance between the id, ego, and superego on the one hand and neutrality "defined phenomenologically" (p. 296), which can easily become a ritualized rigid withdrawal from patients, on the other. He correctly concludes that "neutrality is an attitude, one designed to create an objective, nonjudgmental setting that stresses the principle of psychic determinism" (p. 296).

Giovacchini distinguishes two categories of countertransference (p. 21). Although he believes that there are contributions from the infantile mental life in both types, he labels "homogeneous countertransference reactions" those in which the infantile elements are minimal and which represent average expectable reactions. These are distinguished from "idiosyncratic countertransference responses," which are exaggerated and unique and would not be found if the therapist were somebody else. His anecdotes and clinical vignettes illustrate these types of countertransference rather well, even though of course it is easy to criticize any vignettes that are presented so frankly. In my opinion, Giovacchini is most vulnerable to criticism in his sometimes waffling attitude toward the use of the couch, which I think reflects his wish to blur the distinction between psychoanalysis and psychoanalytic psychotherapy. For example, in one case (pp. 86–87) he "firmly" interrupts the patient in the middle of the second session and suggests that the patient lie down on the couch; in another case (p. 101) he recognizes that insisting on the patient's use of the couch would be a mistake and he does not do so. Here he "decided that I would try to analyze her even though she was not on the couch" (p. 116). This calls for an extended discussion of what is and what is not psychoanalysis; in one instance he was seeing a patient six times a week (p. 124), but this frequency is not explained.

In summary, the author offers an interesting and provocative book, which I recommend with certain warnings to beginning psychotherapists and which experienced psychotherapists will find worth reading. Those psychiatrists who consider themselves psychotherapists will probably find more of value in the book than those who are predominantly in the practice of psychoanalysis because of the nature of the patients discussed and Giovacchini's approach to them; I must admit that I could not gather from the book what the title calls "countertransference triumphs."

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PSYCHOTHERAPY

Ending Therapy: The Meaning of Termination, by *Terry A. Kupers, M.D. New York, New York University Press, 1988, 147 pp., $35.00; $15.00 (paper).*

Psychotherapists and their literature have focused much more on how to begin therapy effectively (e.g., how to foster a therapeutic alliance) than on how to end it effectively. An old adage is that "a good start is half of a race." That may be especially true in psychotherapy, since patients might stop the therapy prematurely if a good foundation is not laid in

the beginning that can withstand the later turmoils of grappling with their conflicts and defenses. Terry Kupers, the author of *Ending Therapy*, is a psychiatrist who teaches in a psychology graduate school program and is also in private practice. He masterfully focuses on the other end of therapy, the theory and practice of good endings. A good ending may not always be "half the race," but for some psychotherapy patients it may be that or more. After all, it is at the end of races when the winners are determined. Slow starters sometimes blossom during good psychotherapy and ultimately are the biggest winners from the process. A skillfully managed termination is probably an essential ingredient of most successful therapies, especially for those which deal with major issues involving earlier separations and losses.

Two factors may largely account for the relative neglect, at least in the literature, of termination issues. First, most therapists, like other psychologically healthy human beings, enjoy developing emotionally close and sharing relationships more than ending such relationships. Therefore, a wish to avoid focusing on the relatively unpleasant termination issues of separation and loss is understandable. Second, Kupers believes that decisions regarding the duration of therapy and when it should end are often based on the patient's finances rather than the patient's diagnosis. Kupers has previously termed this a double standard in mental health treatment (1); patients with more money tend to be offered longer and more intensive psychotherapies, regardless of need. In fact, many patients have the fantasy, at least at some phase of their therapy, that their therapist will let their therapy go on forever, if their money holds out. The possible reality of this is fostered by hearing about media personalities who have been in "psychoanalysis" for 15 to 20 years with no apparent end in sight. Some fear that psychotherapy will become a way of life if it goes on too long and that the therapist will become a substitute for dealing with and investing in emotional issues with others. This might be termed the Wolfman syndrome, after Freud's famous patient, who was passed from Freud disciple to disciple for more analysis and became a type of celebrity in some analytic circles. (Pictures painted by the Wolfman were sold at analytic meetings by one of his famous analysts, for example.)

Kupers discusses several forces in the marketplace that often affect the length of therapy. The therapist who does not have a waiting list and fears he or she will not fill empty time slots may, somewhat understandably, be more likely to suggest longer-term treatment. As more types of therapies and therapists enter the marketplace, which in some cities is already saturated, the tendency to hang onto patients beyond what is truly needed or in their best interests may be especially great. Also, therapists who wish to maintain a certain type of practice, such as having several patients in psychoanalysis, may find themselves recommending that form of treatment to patients who might actually be better suited for and more interested in briefer, less insight-oriented therapies. These therapists might even reduce their usual fees to make several-times-per-week analytic therapy financially possible or more attractive (and possibly seductive) to the patient, who is thereby getting a "bargain." We also should keep in mind that if the only tool the carpenter has is a hammer, everything tends to be treated like a nail. If the therapist knows only one form of therapy (if he or she has not kept up with psychopharmacology, for example), then even round patients may unwittingly or otherwise be pushed toward square therapeutic holes.

One of Kupers's recurring messages is for the therapist to try to recommend the type of therapy that best fits the pa-

tient's needs. Another message is to begin to move toward an end to the therapy when patients seem to be mastering how to do their own psychological work to whatever extent they are able and when they become interested in pursuing a self-analytic, introspective way of life. The myth of reaching perfection or a conflict- or defense-free life through a long psychoanalysis has set psychoanalysis up for much criticism and failure. A "good" result is not really good if perfection is viewed as an achievable goal. Kupers reminds us of Freud's position in *Studies on Hysteria* (2) that psychotherapy should be for neurotic misery, not for everyday unhappiness. It is the therapist's professional responsibility to know when that line is being crossed. We should not expect third-party payers (e.g., an employee's co-workers) to pay for the psychotherapy of unhappiness due to the periodic unpleasant conflicts and defenses associated with continuing to be a human being. We human beings will continue our lives as alloys and never become pure gold, even after the forging and tempering of good psychotherapy or analysis.

Another of Kupers's messages between the lines is that a constructive, planned ending of any type of psychotherapy is preferable to having the sessions just dwindle off and the patient fade away; this may make it more difficult for the patient to return later, if needed, because of guilt feelings or feeling like a failure for doing so. Some patients should probably never terminate their therapy but, as Michael Balint (3) recognized, should come in as needed for life for a dose of the powerful drug called doctor. This may be the best that some patients with hypochondriasis or alexithymia, for example, may be able to do. We should not penalize or stigmatize them for doing their best but recommend therapy without end as their treatment of choice. For others, termination may be a time to discuss the expectation that they might come back and legitimize their coming back later or several more times during crises or developmental watersheds. For still others, a firm termination date, several months or a year or so away, as Freud eventually did in his analysis of Wolfman, may be necessary for patients to confront conflicts that they are psychologically capable of addressing but that they might otherwise perpetually avoid, particularly issues relating to separation, emancipation, autonomy, loss, grief, and death.

This book is logically organized, flows smoothly, and is written in a clear, lively style. Kupers skillfully weaves in many case vignettes from his practice to illustrate theoretical points in a manner that is very reminiscent of Ralph Greenson's talent for shifting between and imbricating clinical and didactic focuses. Kupers provides a nice summary of some central termination issues contained in several of Freud's famous cases. Chapter four includes a succinct review of some of Kohut's self psychology contributions and some discussion of how those affect termination decisions.

The primary audience for this book should be psychiatry residents and other psychotherapy students who are in the early stages of their psychotherapy education. In closing, I will pick one relatively minor bone in an otherwise fat-free and well-conditioned book. The author refers to the recipients of psychotherapy as clients rather than patients. Kupers teaches in a psychology graduate program, so I assume that is where he picked up the terminology. I prefer that individuals with illnesses (which I consider neurotic misery to be, and certainly many incipient biomedical illnesses mimic neurotic symptoms) be evaluated initially in a medical model, at least before they are relegated to what is clearly in our culture a business paradigm of professional interactions, values, and expectations. Third-party payers and social agencies are relatively reluctant to reimburse or expand funding for peo-

ple who are not viewed and labeled as having real illnesses. Kupers and others who view patients as clients might read some Talcott Parsons (4) to better understand some of the sociocultural problems in demedicalizing those who are or may be ill and some of the arguments against the politically well-lubricated attempts of nonmedical practitioners to become the primary business brokers for the mentally ill.

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Object Relations Therapy: Using the Relationship, *by Sheldon Cashdan, Ph.D. New York, W.W. Norton & Co., 1988, 224 pp., $22.95.*

The term "object relations" reminds me of what happens in a sculpture garden at night when there are no people around. Psychologist Sheldon Cashdan cuts this oxymoronic knot, admitting that *human* relations is what it is about, starting with mother and child, as opposed to the libidinal-instinctual Freudian frame of reference. The language of object relations therapy requires a heavy baggage handler in the concepts and definitions department, and the author's summaries of Klein, Fairbairn, Mahler, Kernberg, and Kohut are concise and clear.

Cashdan wants a place in the sun for object relations theory, not just a refuge in the shadow of psychoanalysis, which, he notes, may ultimately be too antagonistic to this particular offspring to share the same habitat. Cashdan does not go so far as Stephen Mitchell in his elegant, path-making *Relational Concepts in Psychoanalysis* (1), although he cites the earlier work of Greenberg and Mitchell (2).

Cashdan writes for students and practitioners of individual, marital, family, and group therapy. The presentation is so structured that it feels pedantic at times, but the vignettes are warm and vibrant. A model of therapy evolves that is a real, flowing relationship within firmly structured boundaries.

Illustrated just enough with case reports, the text presents a phase-specific theory of helping: engagement, projective identification, confrontation, and termination. A good starting place for therapists interested in a brief overview of object relations therapy, this book gives the reader, neophyte or experienced therapist, a nice theoretical framework to test. Basic, clear, and humane, it sparkles with interventions both poignant and powerful. These offset the structural rigidity, the reified concepts, and the "in" terminology that separates pedants from people.

Cashdan, who has written an earlier text on therapy (3), teaches well and treats patients with sensitivity, energy, and humor. If we have to live with terms like "object relations," "projective identification," and "splitting," a book like this helps greatly, showing that the concepts are far, far better than they sound.

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Foundations of Object Relations Family Therapy, *edited by Jill Savege Scharff, M.D. Northvale, N.J., Jason Aronson, 1989, 478 pp., $50.00.*

The editor of this book says that it was written to chronicle the struggle of psychoanalysts to integrate intrapsychic dynamics with family processes. In the 1950s Wynne and others observed role stereotyping peculiar to families that included a schizophrenic patient. It wasn't until concepts of pseudomutuality, projective identification, and repressed unconscious object relations developed that two-generation family difficulties began to be described by using psychodynamic formulations. Parental views of the adolescent and the adolescent's view of the parents came to be seen as distortions caused by transferences. Others interested in families began to make use of theories about projective identification (based on Kleinian object relations theory) in group therapy workshops based on Bion's approach. By 1971, Shapiro and Zinner, both contributors to this book, had published papers on family organization from the theoretical stance of projective identification.

The school represented by the authors of this book, in contrast to the systems approach of most family therapies, is psychodynamic. The authors state that they do not ignore systems but work with conscious and unconscious systems of relationships within individuals and families. They use object relations theory, an individual psychology developed from observation of relationships.

Jill Scharff describes object relations family therapy as nondirective listening and deeply personal communication with unconscious processes. She reports that the interpretations resulting from a personal experience of the family unconscious are likely to be more effective than other interpretations. The process depends on insight and constant work with resistance.

Object relations therapy moves beyond Freud to the interpersonal level. It was derived from study of the early infant-mother relationship. Object relations theory suggests that the infant's primary need is for attachment to a caring person, compared with the classic Freudian theory, which views the infant as struggling with drives (libido and aggression) and attempting to achieve gratification. Object relations theory views the transferences from the infantile period as persisting in the form of distortions of present relationships among family members. Jill Scharff describes the major theorists and their contributions as Fairbairn (types of object relationship and the effect on ego development), Dicks (the unconscious reasons for marital choice), Klein (projective identification derived from the death instinct, which results in ego development from the paranoid-schizoid or depressed positions), and Winnicott (the psychosomatic partnership of the mother and child). She also recounts the way in which Bion used Kleinian concepts to understand small groups and their complex relationships to the leader.

Shapiro and Zinner view families as small groups that deal with developmental problems by mutual projective identification processes and subgroup formations. David Scharff and Jill Scharff contribute views on how transference and countertransference are used in family therapy.

The 24 chapters of this book focus on adolescent development, projective identification in family organization, a description of the group-interpretive approach, the integration of individual and family therapy, and the use of an object relations approach to sexuality. It reprints some previously published papers to give a historical and developmental perspective to object relations family therapy. The chapters by Jill and David Scharff are among those which have not been previously published and are especially well written. They are practical, clinically useful, and illustrated with case examples. This combination of individual, interpersonal, and systems-oriented therapy will be useful to those who wish to understand individual family members as well as the family system.

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Vocational Rehabilitation of Persons With Prolonged Psychiatric Disorders, *edited by Jean A. Ciardiello and Morris D. Bell. Baltimore, Johns Hopkins University Press, 1988, 285 pp., $45.00.*

Walter Neff, a pioneer in the field under scrutiny in this collective volume, clearly defines the tone of the effort. Rehabilitation "is not so much 'curative' as 'ameliorative,' with the aim of bringing the person to a maximal level of functioning *within the limit* of a continuing deficiency of some kind" (p. 7). The other contributors elaborate on the polarities implied here between the therapeutic ideals (maximal levels) and the pragmatic realities (limits) of vocational rehabilitation. The tension is lively and ultimately unresolved, as befitting the current state of this endeavor so crucial to the future of our patients with prolonged psychiatric disorders. The book sums to a substantial and realistic reflection of a field *in statu nascendi*, struggling to define a workable dialectic.

Chapter two outlines with chilling clarity the target population, who, as noted later by Anthony et al., have all too often been taught how to be patients rather than workers by our treatment systems to date. Chapter three specifies some of the goals of rehabilitative work with this population. One set of strategies aims to help the patient fit the environment, e.g., by reducing symptoms, fostering insight into illness or disability, or tempering unrealistic aspirations. Another set aims to match the environment with the patient's limitations, e.g., by anticipating regression, modulating stimulation, or emphasizing easily attainable short-term outcomes. The first set demands adaptation; the second set offers asylum. Although they make strange bedfellows, both are necessary and both receive ample elaboration in the ensuing chapters.

Anthony et al., as usual, provide the most conceptually clear and comprehensive overview about psychiatric rehabilitative models for instrumental disabilities (impaired work functioning may be the most common characteristic of severe mental illness). Their approach balances developing the patient's skills and independence on the one hand and marshalling environmental resources and supports on the other, although their bias seems to rest with the ideal of instrumental autonomy. There is nothing wrong with such a bias (it built

the United States), except that it assumes the presence of capacities which many of the severely mentally ill simply do not possess, such as initiative, drive, ambition, and persistence. Many of the rehabilitative strategies designed up to now, such as social skills training, often assume that patients come with motivation and a capacity to learn. As such, they preselect for health and have little, if anything, to offer patients riddled with deficit psychopathologies. This oversight—a potential Achilles heel to the rehabilitative movement—is apparent in other chapters as well. For example, a chapter about vocational assessment instruments reviews investigations using these tools in the general population because little or no data exist about their application to psychiatric samples. This is a bit like a drunk searching for his lost wallet under the street lamp because that is where the light is.

The chapter by Bond and Boyer reviewing 21 control studies of vocational rehabilitation programs offers a rather stark counterpoint to any glib therapeutic zeal. If the outcome measure is competitive employment, "the general conclusion is that none of the approaches [reviewed] have demonstrated efficacy in helping patients achieve and maintain competitive employment over any sustained period of time" (p. 52). When outcome is paid employment, including transitional and sheltered work, eight of 10 studies show that programs of intensive support coupled with jobs that are not too demanding help patients "function at a level beyond usual expectations" (p. 252). This, plus the finding that vocational gains are often lost after treatment ends, suggests that "supported work programs may be the best way to increase employment rates" (p. 253). The data clearly suggest that patients can respond if given work, but they also need long-term, indefinite support and programs which accommodate to the enduring nature of the disease processes that make up these disorders.

A chapter by Malamud and McCrory describes a transitional employment program at Fountain House in New York City. Fountain House, a clubhouse located close to Times Square, offers a continuum of work experiences for psychiatrically disabled patients in the inner city. The continuum spans prevocational rehabilitation (real work in the clubhouse), voluntary employment, transitional employment (real work in paid employment), supported work, and on-the-job training. Asylum services, such as supervised housing or evening social and recreational activities, are offered as well. The program is highly supportive and allows for movement backward as well as forward on the employment path. The authors document clearly that the process can be very long (up to 5 years or more) and is successful only about half the time. I found the program description very realistic and sobering but also heartening because it documents that a great deal can actually be done.

Equally compelling in its realism, a chapter by McCrory carries the reader into the dynamic dimension of the rehabilitative process at the individual patient level. Rehabilitative concepts are humanized with pithy case vignettes that illustrate patients' uneven, often unpredictable trajectories toward (largely successful) rehabilitative outcomes. The discussion suffers from a dearth of patients who do not do well (and why), although the author does describe typical crises that can be anticipated, including crises engendered by success. Sensitive but practical suggestions about the management of these crises are offered.

There are 17 chapters in all, and like any volume of collected papers, the quality is spotty. Nevertheless, when good, it can be very good. The book also escapes the pitfall of

redundancy so common to edited volumes. All in all, I give it a "yes." It tells us something about where we are with psychiatric vocational rehabilitation and more about how far we have yet to go.

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Theory and Practice of Brief Therapy, *by Simon H. Budman and Alan S. Gurman. New York, Guilford Press, 1988, 402 pp., $30.00.*

This book, which stems from the authors' work in health maintenance organizations (HMOs), presents their view that the practitioner of brief therapy should not be constrained by any narrow theoretical orientation but should be free to choose from the most beneficial aspects of many different psychotherapeutic perspectives. Therefore, the brief therapist should be pragmatic and eclectic, emphasizing current developmental issues in the interpersonal and systemic context of problems. The model resembles a primary care model that includes significant others in addition to the designated patient, and patients may receive many intermittent courses of therapy over their lifetimes.

The authors stress what they call an interpersonal, developmental, and existential perspective, detailing how to establish a therapeutic alliance within one of five possible therapeutic focuses: losses, developmental dysynchronies, interpersonal conflicts, symptomatic presentations, and personality disorders. After four of these focuses are considered in great detail, a separate chapter on treatment of the personality disorders is followed by chapters on time-limited group psychotherapy, time and termination, and, finally, a detailed case transcript.

The writing is clear and easy to read. There are theoretical discussions supported by copious references and followed by extensive and well-described case material.

For the beginner there is much practical therapeutic wisdom in this book that must derive from the authors' many years of astute learning of theoretical material and deftly applying it to clinical work. For example, I found myself nodding my head often at the wisdom of the thought as well as how accurately it applied to the clinical intervention. One example is their discussion of the issue of asking a patient who comes for treatment why he or she came now. From the perspective of the psychoanalytic psychotherapist—short-term (Sifneos, Davanloo, Malan, and Mann, etc.) or long-term—the book has many shortcomings, however.

The authors exaggerate and distort the psychoanalytic perspective to set up a straw man whom they devalue to contrast with the virtues of brief therapy. The book is rife with overt and covert examples; the psychoanalytic notion of cure, for example, is portrayed as rigid and perfectionist, as is the analyst's notion of time. Thus, while attacking and devaluing "pure" theorists, the authors are in the contradictory position of espousing the same thing—except that their theory is all-inclusive pragmatism. Brief therapy can stand on its own; other perspectives do not have to be distorted in its defense.

The possibility that the amount of activity undertaken by the brief therapist may infringe on the patient's autonomy seems to be of little concern to these authors. For example, they state that the therapist should share trial formulations with the patient, quickly involve significant others, actively influence the patient's social system, and give the patient homework assignments. If the patient had a personality disorder these activities would infringe on the patient's self-activation and sense of responsibility and inevitably produce resistance. I suspect the same may occur with many other types of patients.

There is a parallel lack of concern about countertransference. In a book that exhaustively covers every other subject relevant to brief therapy there is only one page on countertransference. I find it difficult to believe that countertransference does not play a much greater role than indicated and that it specifically may be involved in the degree of activity of many therapists.

The authors' perspective on personality disorders is basically to treat one of the five focuses unless the patient's personality traits interfere with concentration on the focus. Although the practical interventions they describe are adequate, their lack of understanding is indicated by their lumping together borderline and narcissistic disorders in the same cluster and using similar techniques for both, unaware that these two differ so importantly that they require different therapeutic techniques.

In summary, we have two very bright, astute, excellent clinicians who have integrated various theoretical approaches into a pragmatic model for brief therapy that is a treasure trove for the beginner because it contains much clinical information. However, for the psychoanalytic psychotherapist its devaluation and distortion of the analytic perspective, its glossing over and condensing of so many difficult issues, such as how countertransference promotes resistance and interferes with patients' autonomy, seriously detracts from the book's value.

The authors' counterposing brief versus long-term analytic psychotherapy raises a very basic question. As scientists are we to pursue the clinical truth wherever it leads or are we to focus on what is cost efficient? I submit that our task is the former and hope that these authors can extend their reach to accommodate this perspective.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Treatment of Behavioral Disorders in Animals

SIR: As part of a survey of naturalistic animal models of psychiatric disorders, I have learned of a number of instances in which abnormal behaviors in household pets and farm animals were examined and/or treated using a neurobiological framework derived from human studies. For example, sleep disorders in dogs have been studied in the sleep laboratory. In addition, a psychiatrist successfully treated a "one-man" dog with ECT; the dog had stopped eating and moving after his master's accidental death.

Most recently, my colleagues and I have treated canine acral lick, a syndrome in which dogs repetitively lick their paws until the skin ulcerates. A series of dogs responded to clomipramine but not desipramine in a double-blind cross-over study (1).

In order to broaden my survey of this area, I would be most grateful if psychiatrists who know of physiological and/or pharmacological treatment of naturally occurring behavioral disorders in animals would share their experiences with me.

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Parkinsonism-Dystonia Syndrome and ECT

SIR: We read with great interest the article by Richard Douyon, M.D., and associates (1) and the editorial by Richard Abrams, M.D. (2) regarding the use of ECT in patients with Parkinson's disease. Recently we treated a woman with parkinsonism-dystonia complicated by the "on-off" syndrome, *DSM-III-R* major depression, and dysthymic disorder. Her dystonia involved the cervical musculature and blepharospasm.

Ms. A, a 57-year-old Caucasian woman, received nine ECTs with the Thymatron instrument, which delivers a bidirectional, brief-pulse (1-msec wide) square wave stimulus. The output current was 900 mA constant, and the maximum output voltage was 460 V. During her nine ECTs she received succinylcholine, 50 mg once, 40 mg six times, and 30 mg twice; methohexital, 60 mg seven times; and protopol, 90 mg twice. The stimulus duration was 2.2 seconds, and the seizure lasted 30 seconds once, 20 seconds on five occasions, 15 seconds twice, and 10 seconds once. Ms. A continued to take the following medicines

throughout: benztropine, 2 mg h.s.; bromocriptine, 5 mg t.i.d.; and carbidopa/levodopa 25/100, 1½ tablets t.i.d.

We evaluated the patient three times: at admission and after the sixth and ninth ECTs. Her respective Beck Depression Inventory scores were 39, 25, and 24; Hamilton Rating Scale for Depression scores were 46, 33, and 19; Parkinson's Disease Rating Scale scores were 22 (stage III), 12 (stage III), and 4 (stage II); Dystonia Movement Scale scores were 9, 1, and 0; and Disability Scale scores were 5, 2, and 1. To control for diurnal CNS dopamine receptor fluctuations and variability of plasma drug levels, ratings were done at the same time of day each time: 5 hours after her second dose of dopamine agonist and 10 hours after ECT.

The short half-lives of the pre-ECT medications make it unlikely that they affected rating scores, although blood levels of antiparkinsonian drugs were not ascertained. Further, repetitive exposure to barbiturates might induce enzymes, hastening antiparkinsonian metabolism and worsening scores rather than improving them.

ECT improved both the parkinsonism and the dystonia in this patient. While these data support the hypothesis of ECT-induced enhanced dopamine receptor sensitivity (1), other explanations are also possible. Patients with parkinsonism and dystonia manifest a presumed relative excess of acetylcholine and, sometimes, a relative lack of dopamine (this patient responded to dopamine agonists, whereas many patients with dystonia respond to dopamine blockers). Cholinergic hyperfunction has been implicated in parkinsonism, dystonia, and depression, and ECT may down-regulate central muscarinic receptors (3). Parkinson's disease with depression is associated with reduced serotonin and 5-hydroxyindoleacetic acid (5-HIAA) (4), which ECT may reverse (3). Dystonia has also been associated with reduced raphe serotonin and 5-HIAA (5). The focal nature and mild degree of dystonia in this patient preclude generalizing about the effects of ECT on dystonia. More data are needed to resolve these issues.

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Lorazepam Treatment of Resistive Aggression in Dementia

SIR: Patients with dementia affecting the frontal lobes are typically quite apathetic and abulic, initiating little behavior and resisting efforts to help them with personal care (1). Such patients may sometimes violently resist any attempts to bathe, dress, or otherwise handle them, although they are not delusional and not aggressive in other situations. We have noted that this form of aggression tends to respond poorly to neuroleptics but in many cases responds to lorazepam, a short-acting benzodiazepine. The following cases are illustrative.

Mr. A, a 65-year-old man with a 1-year history of radiographically confirmed multi-infarct dementia, was well oriented but exhibited prominent frontal lobe signs on examination, including profound abulia, paratonia, grasp and snout reflexes, and poor Thurstone word fluency. He required maximal nursing assistance because of the abulia but was resistive and often physically violent when bathed or otherwise cared for. There was no agitation under other circumstances. A trial of haloperidol, up to 4 mg/day, did not result in any improvement. Haloperidol was discontinued, and lorazepam, 0.5 mg b.i.d., 30 minutes before concentrated nursing care, was begun. Within several days, Mr. A's aggressive behavior had ceased entirely, and his resistiveness had decreased dramatically. Lorazepam has been continued for 17 months, and the patient continues to do well.

Mr. B, an 81-year-old man with a 15-year history of primary degenerative dementia, was disoriented and globally aphasic, with prominent suck and grasp reflexes. He exhibited frequent agitation, which often culminated in his striking at nurses with his fists, but this happened only during care involving physical contact. A trial of thioridazine, up to 400 mg/day, was ineffective and resulted in oversedation. Lorazepam, 1 mg t.i.d., before nursing care, was subsequently begun; since then, Mr. B has been much more manageable and without aggression. He has successfully continued to take lorazepam for 17 months.

In both of these cases, aggression was exclusively a function of resistance to nursing care. This sort of aggression seems quite common, and yet, surprisingly, it has not been specifically addressed in the literature. A greater incidence of aggressive behavior has been noted in frontally impaired patients (1), but this connection to resistiveness has not been mentioned.

Although there are numerous reports of benzodiazepines increasing aggression (2, 3), this effect is in reality fairly infrequent, occurring in less than 1% of patients (4). Other potential problems with lorazepam include sedation, increased confusion, and ataxia. The latter is especially of concern, given the frequently devastating consequences when elderly persons fall. Fortunately, none of our patients has exhibited any of these problems. Generally, we have found that administering the drug 30 minutes before periods of concentrated nursing care gives the best result.

In our experience, such patients usually do not respond to neuroleptics, perhaps because their aggression does not arise from misinterpretation and fearfulness (i.e., psychosis) but is more an attempt to escape from an aversive situation, nursing care being especially disagreeable to the abulic patient. This may explain the efficacy of benzodiazepines, which may decrease the behavioral effects of aversive stimuli (5). Further work is needed to characterize aggression in demented patients so that definitive therapies can be developed.

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JERI FRITZ, M.S.
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New Extension of the *Tarasoff* Decision

SIR: Psychiatrists have felt besieged in recent years with mounting intrusions into the strict confidentiality that is deemed especially essential to psychotherapeutic treatment. There has been a "steady erosion of the limits of confidentiality in the post-*Tarasoff* era, with an emphasis on guarding against public peril at whatever cost to patients' protective privilege" (1). The *Tarasoff* decision promulgated the doctrine that therapists have a legal duty to "pierce the privilege" of confidentiality and use reasonable care to protect an intended victim of violence threatened by the patient. The following case illustrates a startling new extension of the *Tarasoff* ruling, taking the initiative away from the therapist and authorizing a police search of a therapist's treatment records, which reportedly contained information about his patients' violent propensities.

Two young brothers notified police that they had found both of their parents shot to death by an intruder. The brothers were sole heirs to the parents' multimillion-dollar estate. The boys were considered to be suspects. A third party told the authorities that the boys were in therapy with a psychologist whose records were likely to contain incriminating evidence regarding their violent propensities. Asserting that disclosures made during confidential therapy sessions could be made public under the "imminent danger" exception to doctor-patient privilege, prosecutors raided the therapist's office and seized written notes and audiotapes relating to the brothers' treatment. The defendants will claim at trial that only they or the therapist could act to "pierce the privilege" (2).

Psychiatrists are obligated under the *Tarasoff* decision to breach confidentiality when the patient threatens violence, in order to protect intended victims. The case reported here raises the alarming prospect that when the therapist fails to act when a patient poses an immediate threat to readily identified individuals (or when he or she decides that under the circumstances disclosure is unwarranted), a third party complaint to the police may suffice to trigger a search and seizure of the therapist's office records. The legality of this "*Tarasoff* raid" will be determined at the forthcoming trial.

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Borderline Personality and Multiple Earrings: A Possible Correlation?

SIR: Over the past 6 years of my practice, I have made an interesting observation that I would like to share with other professionals in the field. I have been studying patients with borderline personality disorder that I personally saw in my practice, and I have found a strong correlation between having this disorder and having multiple ear piercings per earlobe. All of the patients were young women between the ages of 16 and 32, and their diagnoses were based on criteria from *DSM-III*, including poor social adaptation, impulsive acting out, intense affectivity, poor interpersonal relations, and mood disorders. Of the total of 52 borderline patients I saw during this interval, 44 had multiple earlobe piercings. Seven patients had multiple ear piercings but did not fit the criteria for borderline personality disorder (all were adolescents with the conduct disorder diagnosis), in comparison with several hundred conduct disorder patients without the physical finding.

I am not aware of any similar observation in the literature and welcome any feedback from readers of the *Journal*.

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Fluoxetine and Elevated Plasma Levels of Tricyclic Antidepressants

SIR: Frank Schraml, M.D., and associates (1) recently reported elevated nortriptyline plasma levels in a patient concurrently treated with fluoxetine. We are pleased that others are confirming our report of this interaction (2). However, we believe that it is very important to extend Dr. Schraml and associates' recommendation of caution when these drugs are used concurrently. Caution must also be observed even when a tricyclic antidepressant is started after fluoxetine has been discontinued.

Fluoxetine's active N-demethylated metabolite, norfluoxetine, has a long half-life of 7–15 days; radiolabeled metabolites of fluoxetine have remained in human subjects for more than 20 days (3). Therefore, tricyclic plasma levels may be elevated for several weeks after discontinuation of fluoxetine.

In one of Vaughan's patients (4), side effects, presumably due to elevated tricyclic plasma levels, persisted for several weeks after the patient had taken 20 mg of fluoxetine for only 3 days.

We were recently consulted about a patient whose fluoxetine, 20 mg/day, had been discontinued; desipramine, 100 mg/day, had been started the following day. Seven days later, she experienced severe postural hypotension. The desipramine was discontinued; however, the postural hypotension continued, requiring her to have complete bed rest for 3 weeks. The patient's desipramine plasma level 2 weeks after the discontinuation of desipramine was reported as 314 ng/ml. However, the possibility of cirrhosis has not been ruled out in this patient.

This altered metabolism of the tricyclic antidepressant may result in higher and prolonged plasma levels of the tricyclic after its discontinuation, possibly causing and prolonging adverse effects. This point is of utmost importance, particularly in cases where an overdose of a tricyclic is taken concurrently with fluoxetine or within weeks of fluoxetine discontinuation. Fluoxetine may at least triple tricyclic plasma levels (2). Therefore, if our colleagues are not aware of this interaction, a patient with a seemingly nondangerous overdose of a tricyclic may not be hospitalized and monitored, resulting in a fatality.

If a tricyclic antidepressant is given concurrently with or even weeks after discontinuation of fluoxetine, we recommend starting with one-sixth to one-third of the usual starting dose, with very careful monitoring of the patient and the tricyclic plasma level and much smaller than usual increments in the dose of the tricyclic. It is important to realize that at present we do not know when tricyclics reach a steady state when they are combined with fluoxetine. Fluoxetine may even cause nonlinear metabolism of tricyclics (2). Obviously when fluoxetine is no longer inhibiting the metabolism of the tricyclic, the dose of the antidepressant may need to be increased considerably.

We believe these precautions should apply to all antidepressants that are not monoamine oxidase inhibitors (MAOIs) until more is known about fluoxetine's effects on the metabolism of other antidepressants. At least 5 weeks should elapse before an MAOI is started after the discontinuation of fluoxetine (5).

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JOHN M. DOWNS, M.D.
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Definition of Splitting in Object Relations Theory

SIR: In his overview article, N. Gregory Hamilton, M.D. (1) stated that splitting is a fundamental tenet of object relations theory. He included self psychology under the object relations umbrella, but he defined splitting in a way that is incompatible with self psychology.

For Dr. Hamilton, splitting is a normal developmental event that occurs because infants are overwhelmed by conflicted feelings of love and hate directed toward their mothers. This intolerable intrapsychic state necessitates defensive maneuvers and leads the child to split images (or part images) of mother and self into the good and bad mother and the good and bad self. Later these images must be united into whole objects that are ambivalently cathected. Failure to accomplish this unification is a principal source of much serious psychopathology. Splitting is considered a *uniform* developmental step necessitated by the *fundamental nature of normal* aggressive and libidinal drives. This theory of splitting was developed by reconstructing data from clinical work with patients rather than through observation of infants. Current developmental research disputes the idea that splitting is a normal developmental step (2).

Kohut (3) understood splitting and the libidinal and aggressive drives that necessitate it in a way that is compatible with developmental research, but Dr. Hamilton and others misinterpret Kohut's position. Kohut insisted that aggressive self-assertion and healthy sexuality are an essential part of normal life. These drives often engender conflict, but the conflicts become clinically relevant only when the drives are distorted or intensified by an unsatisfactory caretaking environment. Self psychologists consistently address the impassioned forms of these drives. They work with narcissistic rage and sexuality that is isolated from intimate relationships. This sort of sexuality and aggression is not normative. Rather, it is the breakdown product of both developmental and ongoing difficulties in finding sufficient, sustaining selfobject support.

This point is central: splitting and other symptoms are usually precipitated by disruptions in relationships that the patient requires for maintaining self-cohesion (4). Such a rupture recapitulates traumatic circumstances from childhood, intensifies affect, and provokes intolerable rage. But the patient must also preserve some aspect of the selfobject bond to the frustrating object. Splitting is one of the defensive maneuvers that patients use to cope with these conflicted needs.

For self psychologists, the correct therapeutic intervention ordinarily is to try to understand what caused the rupture, what the intrapsychic and behavioral consequences were, what predisposed the patient to the injury, and what led to the unique defenses and then to repair the rapport. When therapy is conducted using this approach, confrontational techniques recommended by Kernberg (5) and others are generally unnecessary. Worse, confrontation often leads to further dismemberment of the relationship and magnifies symptoms.

There are fundamental theoretical and therapeutic differences that separate self psychology and some other approaches. If object relations theories are united by the realization that our humanness comes into being through relationships, self psychology belongs under that umbrella. The way splitting is understood divides rather than defines the various object relations theories.

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HOWARD S. BAKER, M.D.
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Dr. Hamilton Replies

SIR: Dr. Baker points to a very important area of controversy within object relations theory: does splitting exist as a universal and normal developmental step? In doing so, he has taken a polar position opposing self psychology to the other object relations theories.

Let us begin with areas of agreement. Splitting does exist as an important mental mechanism. In adults, splitting is often called on at times of loss of sustaining objects or loss of self-esteem. These are two important areas of agreement.

Now, for the areas of disagreement. I contend that most theorists agree that splitting is universal and normal in early life, but for different reasons. For self psychology (1), splitting is universal and normal because empathic failures are inevitable—no one has perfect attunement. For Kleinians (2), splitting is universal because of unmanageable drives. Kernberg (3) sees splitting as necessary for handling overwhelming affects, not drives. I have suggested that neurophysiologically determined cognitive inability to hold opposites in mind at the same time can result in splitting, as can other problems.

Dr. Baker is not unique in overstating his polemical position by equating the worst of Kleinian drive theory with all of modern American object relations theory. As I stated in my recent article and elsewhere (4), object relations theories, including self psychology, are not fundamentally compatible with linear drive theory and should not be taken to task for Klein's excesses in this direction.

I do agree, as do most modern theorists, that Klein's view was too singular and not compatible with modern infant research. I also, however, find Kohut's view equally narrow and consequently unsatisfactory. Splitting does not only arise from infant drives, as Klein would have it, or from parental or therapist failures, as Dr. Baker would have it. It seems to me that splitting can occur when affects are overwhelming, when needs are pressing and unmet, when there is a neurophysiologically determined failure of integrative ego function, and when social groups divide themselves around us into black and white camps.

I do not see any need for clinicians or theorists, interested in self and others and in the internalizing and externalizing processes, to divide themselves into diametrically opposed camps on this issue of what causes splitting—nature or nurture. Let us keep studying the issue and see what comes of it in the future.

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N. GREGORY HAMILTON, M.D.
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Role of Anger in Posttraumatic Stress

Sir: The article on Janet by Bessel A. van der Kolk, M.D., and Onno van der Hart, Ph.D. (1) was one of the clearest psychiatric articles I've read for some time. No jargon, very few obtuse psychiatric words, generally modern language—in short, good communication. I felt, however, that there was little overt discussion of the most important emotion that has to do with survival: anger. That is probably what Janet meant by "vehement emotion," but we should call it what it is. The authors used the popular word "stress," which is putting the emphasis "out there" rather than facing the fact that the emotional and physiological reaction is our anger. Very little of what we call stress is not anger, but we do not want to face our own unacceptable feelings.

In working many years with chronic pain patients, many with posttraumatic stress disorder (PTSD), I have seen early childhood trauma in more than 90%. There really seems to be little difference between the reactions in childhood trauma and PTSD. The life threat and resulting anger inhibit many actions by dissociation, because of the ensuing guilt and fear of one's own destructive rage. Repression helps avoid action that might threaten survival.

Why don't we talk openly about anger and accept its value? It is a wonderful and powerful emotion that keeps us surviving. Without a fight we die.

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EDWARD C. NORMAN, M.D.
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Dr. van der Kolk and Dr. van der Hart Reply

Sir: We are grateful to Dr. Norman for his appreciative comments about our article and for the opportunity to further spell out both Janet's and our own understanding of the role of anger in posttraumatic stress. Although Janet wrote extensively about emotions, he did not assign a central role to anger. He distinguished between "sentiments," which regulate adaptive action, and "emotions," mental disturbances that prevent appropriate accommodation to reality (1). Janet emphasized the necessity of taming the excessive excitement that accompanies fear and anger before being able to take effective action. He thought that "making intellectual sense of an unexpected challenge leads to proper adaptation and a subjective sense of calm and control" (2, p. 409). Raw energy

("psychological force") needs to be harnessed by proper assessment of what is going on ("psychological tension") to permit action appropriate to current exigencies and to integrate present reality with preconceived ideas.

An event may become traumatic when one is unable to make sense out of it and take appropriate action to affect its outcome. Janet thought that when people feel helpless, their "vehement emotions," such as rage or fright, interfere with mobilizing a purposeful response (1). His descriptions of the range of these vehement emotions are reminiscent of what Walter Cannon later defined as fight, flight, or freeze responses. In addition to these acute reactions to traumatizing experiences, Janet proposed an early model of state-dependent learning: because memories of these upsetting events are left unintegrated and patients continue on some level to be aware of having failed to react effectively at the first instance, later experiences reminiscent of the prior stress may subconsciously be perceived as a return of that threat and precipitate "somnambulistic crises" in which the patient recapitulates aspects of the traumatic experience (including rage).

Janet saw anger as an emotion that always energizes, sometimes into adaptive action, at other times merely taking the form of a random discharge of pent-up emotions, particularly in the presence of convenient targets (3). He described chronic and severe anger as only one of several potential expressions of the generalized agitation seen in traumatized patients: "one important expression of [posttraumatic] agitation, anger, often becomes delirious" (3, p. 153).

Over time, the central role of anger in trauma has become clearer; when Abraham Kardiner first spelled out the human trauma response to American audiences in 1941, he described persistent anger as one of the hallmarks of posttraumatic stress. Today, there is good evidence that traumatization invariably leads to difficulty in modulating anger. This may range from the "hate addiction" described by Krystal (4) and the grossly disinhibited anger in many traumatized people who live to victimize others (5) to the inhibition of the expression of anger, seen commonly in incest victims and, probably most frequently, in the patients whom Dr. Norman mentions in his letter, those who suffer from chronic pain after an accumulation of traumatic experiences (4).

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BESSEL A. VAN DER KOLK, M.D.
ONNO VAN DER HART, PH.D.
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Comments on Bulimia

Sir: The recent article by Albert Stunkard, M.D. (1), "A Description of Eating Disorders in 1932," presented a detailed clinical description of bulimia as perceived by the psychoanalyst Moshe Wulff. It is worth noting that Wulff also

emphasized the precipitation of this disorder by "a loss of love . . . an insult to the patient's narcissism," the relationship of the disorder to hypersomnia, and patients' generally hysterical appearance and marked mood lability. They seem to closely resemble our description of patients with hysteroid dysphoria (2).

The hypothesis that hypersomnia, hyperphagia, and rejection sensitivity are all manifestations of an unstable appetitive-pleasure and mood-regulatory system related to withdrawal of an amphetamine-like substance is interesting, especially considering the beneficial impact of the monoamine oxidase inhibitors on all aspects of the syndrome (3).

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Sir: Dr. Stunkard's article on eating disorders in 1932 was a notable contribution to the history of psychiatry. Some notes at hand can add to his story.

When one is tracking the early use of words, it is helpful to rush first to the Oxford English Dictionary. Under "bulimy," the OED notes that Trevisa in 1398 described "bolismus" as "inmoderate and unmeasurable as it were an hounds appetyte"; with respect to its variant word "bolisme," "Houndes have contynuall Bolisme, that is inmoderate appetyte."

Like all words, "bulimy" has been modified in form and meaning over the years. "Bulimy" was used before the time of Trevisa, by the Arabs, the Romans, and the Greeks, hence the Greek boulimos, from bous (ox) and limos (hunger), and from this, the Latin bulimus. Gluttony and gorging were well-known in classical times, as was vomiting from the stuffing-in of food.

The term "bulimy" and variants have been used through the centuries to denote insatiable, immoderate, and morbid appetite (usually in "maniacks" and "ideots") as, for example, canine appetite or hunger (appetitus caninus, fames canina).

Those readers who are interested in the history of words should try variant spellings of "bulimy" as noted in the OED and also "adephagia," "bupeina," "cynorexia," "hyperorexia," and the several words about perverted appetite, such as the well-known "pica" and "autophagia," "stercophagia," and other "phagias" from hair to nuts and bolts etc.—i.e., anything!

EDWARD L. MARGETTS, M.D.
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The Antisocial Personality Disorder Diagnosis

Sir: I believe that Linda J. Gerstley, Ph.D., and associates (1) raised an important issue that should be addressed before DSM-IV is carved in stone: what is a psychopath, and how does that diagnosis relate to the DSM-III-R diagnosis of antisocial personality disorder?

When I was trained in the use of the Washington University criteria (2) in the mid-1970s, I was told not to give a diagnosis of antisocial personality to a patient whose antisocial behavior developed after or concurrently with a drug abuse problem. The implication was that drug abuse may lead to antisocial behavior but that the drug abuser might not have an antisocial personality. The diagnostic strategy was to capture the antisocial personality with operationalized criteria because inner psychological mechanisms could not reliably be ascertained, but the core concept of psychopathy—the extended narcissism noted by Cleckley (3) and others—was retained.

After several years in a forensic setting, I came to a conclusion about the DSM-III diagnosis of antisocial personality disorder: the syndrome thus described is a behavior pattern that can be associated with a number of personality disorders. One would normally expect to see a "criminal" personality structure (4), with narcissistic and hysterical patterns also common. However, I have seen borderline personalities, "disturbed children" acting out as adults, and the old "dyssocial" types of personalities associated with what I have come to call the antisocial behavior disorder, which belongs, I think, on axis I.

Does the constellation of behaviors in the DSM-III-R diagnosis of antisocial personality disorder have any utility? I think that it does. In DSM-I terms it would be an antisocial "reaction." The collection of behaviors occurs relatively often and gets the person into difficulties. However, whether the syndrome is conceptualized as a clinical disorder or is given a V code (it is often "the focus of attention" [DSM-III-R, p. 359]), it belongs on axis I.

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Mania After Nicotine Withdrawal

Sir: The mania of the patient in a case recently reported by Franco Benazzi, M.D. (1) may well have been precipitated by nicotine withdrawal. However, before one can firmly make this assumption, further data are needed. 1) What was this man's premorbid personality (cyclothymic etc.)? 2) What was his emotional status during the years he was a smoker? 3) What, if any, nicotine withdrawal symptoms did he experience?

Untoward results certainly may occur with cessation of smoking (2). It may often be necessary to treat associated psychiatric symptoms (3). If the patient is drinking more than the equivalent of two to three cups of coffee a day, it is advisable to reduce the caffeine intake; otherwise, anxiety will mount when nicotine is discontinued. Antidepressants

(4, 5) and benzodiazepines may be helpful adjuncts in smoking cessation.

The possible role of renal dialysis in the case report was unclear, with seemingly contradictory statements: 1) "Ten days before the appearance of these symptoms he had started dialysis" and 2) "significant changes in the patient's behavior had been observed by his wife well before he first started dialysis."

Until these points are clarified, the relationship between smoking cessation and mania in this man remains conjectural.

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Dr. Benazzi Replies

SIR: Dr. Cohen would like to know about this patient's premorbid personality, emotional status during the years he was a smoker, and nicotine withdrawal symptoms. In a further interview with the patient and his wife, I obtained the following data. He had always been quiet, stable, light-hearted, and a little suspicious. He had no personal and family history of psychiatric disorders. He had started smoking when he was 8 years old (he was 57 years old when he stopped smoking and developed mania). Soon after nicotine withdrawal he experienced the symptoms of craving for nicotine, irritability, anxiety, and difficulty concentrating.

Dr. Cohen states that I made contradictory statements about the role of renal dialysis in the development of mania in this patient. I don't think I made contradictory statements. In fact, in the case report I stated that "the clinical picture of mania with psychotic features" [italics added here] was observed 10 days after he had started dialysis, but manic symptoms (irritability, insomnia, hyperactivity, difficulty concentrating) had appeared some weeks before dialysis was started and after nicotine withdrawal.

FRANCO BENAZZI, M.D.
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Partial Hospitalization and Psychotic Patients

SIR: In their recent article, Susanna Parker, M.D., and James L. Knoll III, M.D. (1) asserted that "partial hospitalization is as effective as inpatient care in treating psychotic patients who do not present an imminent risk of violence." To support this assertion, they cited two randomized, controlled trials that compared partial hospitalization with inpatient care (2–4). Close inspection of these studies reveals that Drs. Parker and Knoll's generalization is unwarranted.

In the first study (2), Zwerling and Wilder randomly as-

signed a group of newly admitted hospital patients to day hospital treatment, which lasted for a median of 2 months, or inpatient care, which lasted for a median of 3 weeks. Of the schizophrenic patients assigned to partial hospitalization, 40% were treated without transfer to full hospitalization, 36% were transferred, and 24% were rejected from partial hospitalization. Patient and family factors were the most common reason for transfer or rejection. Behavioral symptoms observed by the day hospital psychiatrists accounted for only 6% of the schizophrenic patient rejections and only 4% of the schizophrenic patient transfers. Most of the schizophrenic patients who were transferred for inpatient care were transferred during their first day of partial hospitalization, and most of these transfers were for more than a week in duration (2). At 2-year follow-up (3), the results were quite mixed. A trend toward poorer outcome for the partial-hospitalization patients was apparent in the male schizophrenic subsample, who had experienced earlier and more frequent hospitalizations, greater unemployment, and lower self-ratings than their inpatient counterparts. For the female schizophrenic patients, the rate of rehospitalization was lower for the partial- than for the full-hospitalization group. Unfortunately, no specific measures of functional outcome were presented to reinforce this finding.

In the second study (4), Herz et al. randomly assigned a carefully selected group of patients, after an average of 3 inpatient days, to either day treatment or continued inpatient care. More patients were excluded because they were too disorganized or lacked family (N=91) than because they were perceived to be at risk for suicidal or violent behavior (N=75). These and other exclusion criteria resulted in a study sample with only a small minority of patients who had had two or more previous hospitalizations (15% in the partial-hospitalization group and 27% in the full-hospitalization group). Because no analyses were presented for the psychotic or schizophrenic subsamples, this study does not permit one to draw conclusions about the relative efficacy of partial and full hospitalization for psychotic patients.

In their update, Drs. Parker and Knoll provided an informative analysis of the complexities behind the underutilization of partial hospitalization. However, beyond the important professional, attitudinal, and financial barriers identified by the authors, important questions about efficacy remain to be adequately addressed. Specifically, the clinical indications and contraindications for partial hospitalization remain to be well defined by rigorous empirical study.

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New York, N.Y.

Dr. Knoll and Dr. Parker Reply

SIR: Dr. Olfson's comments are obviously well researched and well thought out, and we are in full agreement with him. It should be noted that our article was reviewing the literature and not necessarily testifying to its validity. The two studies on partial hospitalization of psychotic patients referred to by Dr. Olfson were flawed in that they excluded patients who lacked a stable family/environment support system. However, it should also be noted that this is one of the major indications for partial hospitalization. We certainly support the call for more rigorous empirical study. Our position, however, is that until the "important professional, attitudinal, and financial barriers identified by the authors" are overcome, these studies will be hard to perform. Unfortunately, rigorous empirical studies are exactly what is needed.

JAMES L. KNOLL III, M.D.
SUSANNA PARKER, M.D.
Dallas, Tex.

Comments on Process Theory and Psychiatry

SIR: I would like to point out two serious errors in logic in the article by Hector C. Sabelli, M.D., Ph.D., and Linnea Carlson-Sabelli, R.N., M.S., applying Heraclitus's process theory to psychiatry (1).

First of all, we must recognize that while we are being offered a theoretical approach to understanding our patients, it is only theory and, as such, unprovable. Godel (2) was able to show that consistency does not indicate validity. Dr. Sabelli and Ms. Carlson-Sabelli indicated a number of times how well their approach "works," which is an indication of consistency but not validity. If one looks at information a certain way and draws the conclusion that the data support the interpretation, one has achieved consistency but not validity.

The second error is the authors' demonstration of differences between process theory and conflict theory. Viewing conflict theory through the glass of process theory, they find conflict theory insufficient for understanding and managing patients. This is like using Euclidian geometry to validate Lobochevski's views about parallel lines meeting. If we accept Euclid's axioms and postulates and view space as planar, Lobochevski is "wrong." If we accept Lobochevski's axioms and postulates and view space as curved, then Euclid was "wrong" (3). The error in logic is that each system is internally consistent yet cannot be used to determine another system's validity.

While process theory appears to have value for the practicing psychiatrist, for the reasons I have mentioned one cannot state that it has value *over* other approaches. The ability to change approaches on an as-needed basis is the essence of eclecticism. The ability to use varying and possibly incompatible approaches, rather than the inability to do so, is generally more helpful for patients, not forcing the situation to fit the *Weltanschauung* of the psychiatrist. The authors' example of depression treated "only" with psychopharmacological agents is a good example. As they put it, "Psychopharmacological treatment without psychotherapy implies a materialistic theory of biological psychiatry in which mental dysfunctions are simply biological illnesses." While a more holistic approach is theoretically desirable, there are indeed patients who do not wish to involve themselves in psycho-

therapy and yet do quite well with psychopharmacological treatments alone. The doctor-patient relationship implies that the doctor and the patient decide on the course of treatment together and agree on how the process of treatment will be understood. The statement I have quoted is not indicative of respect for the patient's point of view. The article's case report seemed to me to show that respecting the patient's view of himself or herself is more beneficial to the outcome of a therapeutic endeavor than forcing the patient to fit into a preexisting paradigm in the psychiatrist's mind. The paradox, then, is how to approach a patient in a framework of understanding and yet understand the patient's concerns on his or her own terms. The resolution of this conflict, if you will, is the creation of the therapeutic alliance, which has been demonstrated to be one of the essential factors in a successful outcome of treatment (4).

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DOUGLAS A. LANDY, M.D.
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Dr. Sabelli and Ms. Carlson-Sabelli Reply

SIR: We confess to Dr. Landy that we have committed the twin errors of rethinking critically our assumptions, rather than accepting them unconsciously or dogmatically, and of attempting to test one theory against another through experiments and clinical observations. Theories cannot be proven but can be supported or refuted. Theories suggest how to collect relevant data for both research and clinical purposes.

Freud defined depression as anger turned inward, and Cannon saw fight or flight as alternatives. Process theory conceptualizes anger, fear, and discouragement as coexisting, opposing, and complementary responses to conflict (1). Longitudinal studies (2) indicate that rage, anxiety, and depression are positively correlated. This experimental evidence for the conflict theory of affect indicates the need 1) to search for and treat the conflicts that may be the cause of anxiety or depression and/or the result of the conflictual behaviors produced by affective disorders of metabolic origin and 2) to treat anger when treating anxiety or depression, and vice versa.

We developed a bifurcation model for bipolar illness that accounts for many of its clinical features and suggests specific therapeutic interventions (3). Bipolar illness is often seen as resulting from the failure of neuroamine synaptic transmitters to restore homeostatic equilibrium (point attractor model) or as an excess of endogenous rhythms (periodic attractor model). Process theory suggests that bipolar illness results from an increase in the flow of physical energy in the brain, resulting in an increase in flows toward equilibrium in point attractors (hyperreactivity of defenses), periodic attractors (diurnal, monthly, seasonal, and idiosyncratic cycles), and chaotic attractors (psychological and marital storms;

psychoses), which in turn produce novel and complex "dissipative structures" (enhanced creativity in hypomanic states; creation of psychotic delusions and personality dysfunctions).

Recognition that biological and psychological processes are aspects of the same process can guide research on diagnosis and treatment, suggesting a fixed relation between affect and synaptic activity. Acetylcholinergic substances have been shown to trigger rage in cats, and we are successfully using atropinic cholinergic blockers to treat marital (4) and other forms of hostility. By monitoring phenylacetate excretion, we appear to be able to characterize a form of depression and to differentiate depression with panic attacks from pure panic disorder (5). We found phenylacetate excretion to vary synchronously in divorcing spouses (3), which illustrates our concept of the supremacy of the complex, i.e., how psychological processes can dominate biology (1).

The comprehensive approach to psychiatry implied by process theory does not hinder the patient's freedom to choose treatment but highlights the psychiatrist's responsibility to indicate when biological, family, or individual therapies are needed. Ethical considerations should prevent clinicians from treating biological illness with psychotherapy only, personality dysfunctions with psychopharmacology only, or marital conflict as an individual dysfunction. Colleagues renowned as psychopharmacologists do excellent psychotherapy through the act of prescribing.

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HECTOR C. SABELLI, M.D., PH.D.
LINNEA CARLSON-SABELLI, R.N., M.S.
Chicago, Ill.

Psychotherapy Training for Residents

SIR: As someone who has been involved in both residency education and psychotherapy teaching for several years, I read with interest the report of the joint task force of the Association for Academic Psychiatry and the American Association of Directors of Psychiatry Residency Training on psychotherapy training for psychiatric residents (1). I feel that their recommendations were overall quite balanced and should be acceptable to a broad range of psychiatrists. I would, though, like to present an additional idea for consideration and possible implementation.

It seems clear, as the authors of the report suggested, that as the biological model has become more prominent, there has been a general erosion in psychotherapy skills among younger psychiatrists and trainees. Except through postgraduate psychoanalytic training or such things as family therapy training institutes, there is no organized way to obtain further intensive training in psychotherapy. Additionally, although there has been discussion in the psychoanalytic community about the interface and overlap of psychoanalysis and the other psychotherapies, the psychoanalytic institutes, in general, teach from a pure psychoanalytic model.

Therefore, I suggest the organization of fellowship training programs in the psychotherapies that would span 2 years and provide wide-ranging, intensive training in psychoanalytic, supportive, family, and group therapies. This would help to create a group of psychotherapy subspecialists who could provide treatment and supervision for a broad range of patients.

As more of our patients are treated with multiple modalities (combinations of medication and psychotherapies), care is often fragmented, with psychotherapy provided by one clinician and medication by another. My personal experience has suggested that this arrangement is far from optimal. The training I am suggesting would create a group of psychiatrists uniquely prepared to provide comprehensive treatment of these patients.

I feel that this is an idea whose time has come, and I would be interested in any feedback from the authors of this report or from the general psychiatric community.

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SIR: It was gratifying to read the article on psychotherapy training for the psychiatrist of the future. The authors are to be commended for taking a forthright and positive stand regarding the place of insight-oriented, dynamic psychotherapy in the training of psychiatric residents and for proposing a curriculum that seeks to make possible this important experience.

Valuable as the article by Dr. Mohl and associates is, there are several points pertaining to this general topic that I believe deserve special emphasis.

1. Insight-oriented, dynamic psychotherapy is not simply one of the many forms of treatment available in psychiatry today; it is intimately related to the substance of the doctor-patient relationship as it applies to our field.

2. Experience in doing fairly intensive dynamic psychotherapy is essential if residents are to understand the meaning of basic concepts such as transference, countertransference, and therapeutic alliance. In the abstract, these remain just words, and their importance is not learned by doing only short-term, supportive work. In a similar vein, established psychiatrists cannot claim to be psychotherapeutically informed or equipped to supervise others in the area of psychotherapy unless they actually practice what they supervise (surgeons learned long ago that they need to spend time in the operating room, every day).

3. The proposal by Dr. Mohl and colleagues for a psychotherapy curriculum is, in fact, quite conservative. They suggest that each resident spend a minimum of 200 hours treating patients with dynamic psychotherapy. That amounts to about 1 hour per week over 4 years, or about 1.3 hours per week over 3 years. This is very little. One would not

expect someone to learn how to play tennis or the piano by practicing only an hour a week; one wonders how that could be enough to learn psychotherapy. Also, the authors estimate that approximately 13% of the residents' training time should be devoted to learning psychotherapy. It would have been helpful if the authors had spelled out how the remaining 87% of their time ought to be apportioned, at least in broad categories. Residents really struggle to find time in their crowded days for everything they need to do and want to learn, and they seek guidance in how to put it all together.

I remember that when I was a medical student, Elvin Semrad (then a prominent teacher of psychiatry in Boston) told us that if we wanted to learn about psychiatry, we should each "buy a good suit with two pairs of pants [he emphasized with his voice the word 'good'] and then plan to sit with patients until we had worn through the seat of both pairs." One wishes things could be that simple again.

PIETRO CASTELNUOVO-TEDESCO, M.D.
Nashville, Tenn.

Sir: The Special Article on psychotherapy training for the psychiatrist of the future has stirred us to reply with a letter of commendation. We too are concerned that with the current explosion of psychiatric knowledge, psychodynamics may become underemphasized in psychiatry residency education, and psychotherapy training may become an elective experience. We note that psychiatric residents, in addition to psychiatric educators, debate whether psychotherapy should be taught to psychiatric residents (1–4).

Our sole disagreement with Dr. Mohl and associates is that they presented a model curriculum with minimum training in psychodynamic psychotherapy for resource-poor programs. We feel that the original model curriculum should be the minimum curriculum!

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Greenville, N.C.

Dr. Mohl and Associates Reply

Sir: We have no disagreement with Dr. Schwartz's recommendation of fellowships in psychotherapy training. With the reduction of time spent on psychotherapy education in general residency, this seems to be a likely "growth area" for psychiatric educators. We want to be sure, however, that all psychiatrists have the minimum experience in psychotherapy, in order to accomplish the various goals outlined in our article and emphasized in the letter from Dr. Castelnuovo-Tedesco.

We appreciate Dr. Castelnuovo-Tedesco's underscoring and elaboration of two of the more important rationales for our proposal, which is indeed a conservative one in terms of the total number of hours devoted to psychotherapy. It is an unfortunate reality that many programs will not be able to provide more than this basic exposure. While we cannot answer the question about how residents spend the remaining 87% of their time, if a program meets all the requirements of the essentials, at least that much time is spent meeting the other requirements.

We also agree with Dr. Finestone and colleagues that the original model curriculum *should* be the minimum curriculum, but the curriculum for resource-poor programs is an attempt to speak out for a minimum standard in an imperfect world.

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Boston, Mass.

Further Views on Patient-Therapist Sex

Sir: I was amazed by the accusatory tone and content of the letter from Judith V. Jordan, Ph.D., and colleagues (1) in response to the article by Thomas G. Gutheil, M.D., on patient-therapist sexual misconduct (2). While we all agree on the need to avoid blaming the victim, the treatment of patients with severe developmental disorders and life trauma involves developing a context for dialogue. There is no doubt that diagnostic categories may have stigmatizing connotations and can be used in a reductionistic manner to discount the social causes of illness. The leprosy of yesteryear and the AIDS of today are diagnostic categories that have been misused in this way (3). The solution to such fallacies is to address the potential for such errors and biases in ethical and clinical reasoning as a central part of graduate, postgraduate, and continuing education (4, 5), rather than to deny the aspects of clinical reality about which Dr. Gutheil wrote.

I have heard also from female supervisees about female patients' demands for sexual contact, and it is clear that an understanding of such demands, rather than acting unethically or reacting moralistically, is what is needed. This requires exploration of the unique aspects of the patient's experience and the therapist's countertransference feelings as well as therapeutic alliance building. Supervisees who have received training in mental health ethics seem particularly apt to put such supervision to good use.

Resorting to gender-specific stereotypes in response to ei-

ther patient illness or therapist misconduct advances neither the goals of treatment nor feminism any further than the biases unjustifiably attributed to Dr. Gutheil. As a colleague and coauthor for more than a decade, I speak with some confidence about the lack of foundation for the accusations made against Dr. Gutheil.

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HAROLD J. BURSZTAJN, M.D.
Cambridge, Mass.

SIR: I write with respect to the recent correspondence concerning Dr. Gutheil's article on patient-therapist sex. As a philosopher, ethicist, and feminist, I believe it is worth noting that Dr. Jordan's view that Dr. Gutheil is guilty of blaming the victim is unfounded. Whether or not Dr. Gutheil's descriptive claims about patients are true, it does not follow from them (logically) that he blames patients. For Dr. Gutheil to be blaming patients, he would have to add premises to his descriptive account, premises of a very different kind from the descriptive ones that he has advanced. He would have to add evaluative (normative) premises, such as 1) women patients who behave in seductive ways with their therapists act wrongly, and 2) women patients who act wrongly in therapy are blameworthy. On my reading of his article, he claims neither. To infer from his descriptions of patients that he is blaming the victim is to attribute to him views for which there is no evidence that he holds.

Were we to saddle Dr. Jordan and her colleagues with the same line of reasoning that they deploy in their attack on Dr. Gutheil, the same moral indignation could be directed at them as they have directed at Dr. Gutheil. Consider the following. They suggest that Dr. Gutheil should "think more about the difficulty these women have in protecting themselves from revictimization." White South Africans defend apartheid on the grounds that black South Africans cannot take care of themselves. A similar line of reasoning was used to justify slavery in America. Furthermore, much sexism is based on the assumption that women are unable to take care of themselves. The alleged inability of people to take care of themselves has frequently been invoked to justify oppressing them. I am certain that Dr. Jordan and her colleagues do not wish to oppress the victims of sexual misconduct, but this is only because I do not infer from their descriptive claim—that the victims of sexual misconduct experience difficulty taking care of themselves—a prescriptive claim—that their wishes ought to be discounted.

Finally, it is worth mentioning that one of the points which feminist theorists have repeatedly made about sexism is that it is particularly successful in oppressing women precisely because women internalize the messages conveyed by a sexist society and become their own oppressors. That is, in accor-

dance with social stereotypes, they cultivate a "waif-like demeanor," "manipulative skills," and so on, which they ultimately use to their own detriment. To diminish the importance of the psychopathology involved in self-oppression, as Dr. Jordan and her colleagues do, is also to diminish the recognition of the harm experienced by women in a sexist society and, ultimately, to weaken the legitimate claims of feminists. Given this, Dr. Gutheil's unflinching description of the role that some women patients play in becoming their own oppressors can be viewed as strengthening feminist arguments. He should be celebrated rather than scorned.

PATRICIA ILLINGWORTH, PH.D.
Montreal, Que., Canada

Dr. Gutheil Replies

SIR: I am delighted that at least one reader—like myself, feminist in orientation—has grasped the point I was driving at. While I could not have expressed the point with Dr. Illingworth's clarity, cogency, or conceptual force, I quite agree with the implication that the critics she mentions seem insufficiently attuned to the antifeminist dimensions of their argument.

THOMAS G. GUTHEIL, M.D.
Boston, Mass.

Differential Diagnosis of Multiple Personality Disorder

SIR: In an exchange of letters to the Editor (1), J.M. Rathbun, M.D., and P.K. Rustagi, M.D., pointed out that the *DSM-III-R* criteria for schizophrenia can lead to the misdiagnosis of patients with multiple personality disorder because both disorders have auditory hallucinations, and Kenneth S. Kendler, M.D., and associates replied that multiple personality should be added to schizophrenia's differential diagnosis in *DSM-IV* but rejected any modification of schizophrenia's diagnostic criteria because, they said, multiple personality is a relatively rare disorder. However, it was not so long ago that child abuse was considered rare, and we might be making the same mistake with regard to multiple personality. Although most psychiatrists still think of multiple personality as a disorder that is rare but obvious, clinicians familiar with it say it is not rare, only rarely obvious (2, 3). What is indisputably rare is the psychiatrist who ever considers the diagnosis.

Before I learned about multiple personality disorder, I had treated a number of these patients for years without realizing that they were examples of multiple personality. Some of them met the diagnostic criteria for schizophrenia, a disorder whose supposed prevalence has had a reciprocal relationship with the recognized prevalence of multiple personality (4). Others of these misdiagnosed patients with multiple personality seemed to have a mood disorder with psychotic features or borderline personality disorder—the other two disorders that, along with schizophrenia, appear in the *DSM-III-R* differential diagnosis of multiple personality. I am happy to see that Dr. Robert Spitzer, who chaired the *DSM-III-R* task force, thinks that multiple personality, even if assumed to be rare, belongs in the *DSM-IV* differential diagnosis of disorders with which it may be confused. Maybe then, with more than a rare psychiatrist considering the diagnosis of multiple personality, we'll get a better idea of its true prevalence.

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Multiple Personality Disorder in India

SIR: In their recent article entitled "Current Status of Multiple Personality Disorder in India" (1), Adityanjee, M.D., and associates commented on the rarity of multiple personality disorder in India, where the possession syndrome is commonly reported. In the Western world the reported incidence of these syndromes is reversed. One reason given by Dr. Adityanjee and associates for this variance is that in the West, possession syndromes may be "lumped together" with multiple personality disorder. This is probably true. Indeed, the main differences in these dissociative syndromes seem to be only in terminology and cultural and scientific beliefs.

In the West the phenomenological similarity of possession and multiple personality disorder has long been appreciated (2). When belief in possession was strong, cases of multiple personality disorder were probably diagnosed as possession (3). It was only when belief in possession subsided at the end of the eighteenth century that case histories labeled as multiple personality disorder began to appear in mesmerist writings and later in the medical literature (3). After this change, when nonpsychotic persons exhibited signs of possession and believed they were possessed by a spirit or other entity, they were diagnosed as having multiple personality disorder if they otherwise met criteria for this diagnosis.

What then is the difference, if any, between possession and multiple personality disorder? Oesterreich (4) said that the most striking characteristic of possession is that "the patient's organism appears to be invaded by a new personality; it is governed by a strange soul." This description generally fits multiple personality disorder as well (3). In this disorder the personalities frequently believe that they are distinct and separate persons or entities (spirits, demons, etc.) which somehow occupy the same body. It is not uncommon for the personalities to explain this odd occurrence by the belief that they or other personalities are entities (spirits etc.) that have "possessed" the body.

Furthermore, possession is subdivided into two types: lucid and somnambulistic (the person has no memory of the episode). It may be overt (manifest) or latent, involuntary (spontaneous and unwanted) or voluntary (deliberately produced and wanted). Examples of the voluntary type are some practices of shamans and spiritists/mediums (4). These terms, with the possible exception of voluntary possessive states, apply equally well to multiple personality disorder (3).

Therefore, the only fundamental difference between multiple personality disorder and so-called possession may be in the voluntary type. Since it only reflects whatever belief system happens to be current, neither term—multiple personality disorder or possession—is adequate to explain all the varieties of these phenomena.

William James's statement that a serious study of these phenomena is one of the greatest needs in psychology (2) still holds true. However, we believe that our present diagnostic classification is not adequate for a comprehensive study of these multiple identity phenomena and therefore should be revised.

We also want to point out that there was a case of multiple personality reported from India (5) which was not mentioned in Dr. Adityanjee and associates' article, bringing the total number of such cases before their own to three, instead of two as they stated.

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ALLEN O. BATTLE, PH.D.
Memphis, Tenn.

SIR: Dr. Adityanjee and colleagues attempted to provide a valuable cross-cultural prospective on dissociative disorders. Unfortunately, the attempt failed because of a lack of diagnostic rigor. Of the three cases they presented, the second and third clearly did not meet the *DSM-III-R* criteria for multiple personality disorder because there was no *repeated* alternation of control. These cases appear appropriate for the diagnosis of dissociative disorder not otherwise specified.

Given our fragmentary state of knowledge regarding the dissociative disorders, careful attention to diagnostic rigor seems indicated.

J.M. RATHBUN, M.D.
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Dr. Adityanjee Replies

SIR: My coauthors and I thank Dr. Downs and associates for their useful and interesting comments on differences between multiple personality disorder and the possession syndrome. Their views, indeed, are a reiteration of our earlier opinion that these syndromes reflect parallel dissociative disorders with similar etiologies despite some differences in clinical profiles. We agree with their assertion that our present diagnostic classification is inadequate for a comprehensive study of these multiple identity phenomena and therefore needs revision. The current ambiguity is beautifully demonstrated by the position taken in *DSM-III-R*, which states that the belief that one is possessed by another person, spirit, or entity may occur as a symptom of multiple personality disorder. In such cases the complaint of being "possessed" is actually the experience of the alternate personality's influence on the person's behavior and mood. Such a position

obliterates any diagnostic differences between multiple personality disorder and the possession syndrome. Indeed, it has been argued that the possession syndrome is not specific to any culture, and its manifestations may differ from one culture to another (1). If that is true, then multiple personality disorder would probably be another culturally influenced presentation of the possession syndrome. Varma et al. (2) believe that the preoccupation of Western society in recent times with role playing as the central guide to molding one's life may be implicated in the pathogenesis of multiple personality disorder. The role adopted, as in multiple personality, does not copy a nonconcrete individual but represents an expedient or expected behavior conceived for a particular setting (2). In contrast to this, polytheism and belief in reincarnation and spirits may be related to greater prevalence of the possession syndrome in India (2).

To our knowledge, no studies have been done so far on the comparability and nosologic similarity of the possession syndrome and multiple personality disorder. Consequently, current diagnostic classifications remain inadequate, as they are based on a one-sided viewpoint.

We further thank Dr. Downs and colleagues for bringing to our notice another case of multiple personality disorder reported from India. This particular report further adds to the current ambiguity, since it brings forth the element of "reincarnation syndrome," which has not been discussed hitherto in the differential diagnoses of multiple personality disorder or the possession syndrome.

We also appreciate the concern expressed by Dr. Rathbun about the lack of diagnostic rigor in the second and third cases described by us. All three patients were seen, diagnosed, and managed in the pre-*DSM-III-R* era; hence our lack of adherence to *DSM-III-R* guidelines. It is true that *DSM-III-R* classifies incomplete forms of the disorder as dissociative disorder not otherwise specified. However, such diagnostic nitpicking may be undesirable, because patients with multiple personality disorder often present with subtle dissociative signs and symptoms rather than the clear-cut overall picture typically associated with the disorder (3). Some of these patients conceal their condition; therefore, the diagnosis may have to be based on indirect manifestations

(3). Indeed, *DSM-III-R*, instead of differentiating multiple personality disorder from dissociative disorder not otherwise specified, seems to acknowledge a dissociative continuum with a range of forms for multiple personality disorder. A similar opinion has been expressed by Kluft (4), who believes that "what is essential to multiple personality disorder across its many presentations is no more than the presence, within an individual, of more than one structured entity with a sense of its own existence." Kluft's continuum leads one to believe that patients with incomplete forms still have the basic underlying structure of multiple personality disorder (3, 4).

Furthermore, lack of repeated alternation of control in the patients we described is explainable by the prompt psychiatric intervention sought by the family members and the correct diagnoses on first contact, in stark contrast to the average delay of 7 years between first presentation and correct diagnosis in Western studies. Moreover, we did not choose to reinforce the symptom and thereby avoided the iatrogenic element, as has been stressed earlier (5). Too-rigid adherence to contemporary diagnostic classifications would have stifled the cross-cultural approach that we adopted in our report.

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ADITYANJEE, M.D.
London, England

Reprints of letters to the Editor are not available.

Highlights of the 143rd Annual Meeting

The 143rd Annual Meeting of the American Psychiatric Association was held in New York, New York, May 12–17, 1990. The total registration was 15,991, including 8,298 members; 1,781 spouses, other family members, and guests; 3,733 nonmembers; 1,642 exhibitors; 406 members of the media; and 131 staff members.

Opening Session

The Opening Session was called to order by Herbert Pardes, M.D., 118th President of the Association, on Sunday evening, May 13, in the Javits Convention Center. Dr. Pardes introduced Dr. Billy Jones, an APA Fellow and Commissioner of Mental Health, Mental Rehabilitation and Alcoholism of New York. The Mayor of New York City, The Honorable David Dinkins, was unable to attend and sent Dr. Jones as his representative. Dr. Jones offered official greetings to the membership and presented Dr. Pardes with a plaque proclaiming May as "Mental Health Month" in New York.

Dr. Pardes introduced the people seated on the stage with him: the members of the APA Board of Trustees, officers of the APA Assembly, and past Presidents of the Association. Dr. Pardes then recognized members of the audience that included the members of the Assembly Executive Committee; past Speakers of the Assembly; past Vice-Presidents of the Association; newly elected national officers, trustees, and Assembly officers; presidents of APA district branches; chairpersons of APA councils, commissions and joint commissions; and the APA Medical Director. He then thanked the members of the Assembly for their hard work and dedication.

Allan Tasman, M.D., chairperson of the Scientific Program Committee, and Philip R. Muskin, M.D., chairperson of the Local Arrangements Committee, were introduced and thanked by Dr. Pardes.

Dr. Pardes then introduced the following distinguished representatives of psychiatric and other related organizations from the United States and abroad:

Representatives of Organizations in the United States: Dr. George H. Allison, President, American Psychoanalytic Association; Dr. Jambur Ananth, President, American Association of Psychiatrists from India; Dr. David Annuziato, Representative, American Academy of Pediatrics; Dr. Hrair M. Babikian, Immediate Past-President, American Academy of Psychoanalysis; Dr. Allan Beigel, President, The American College of Psychiatrists; Dr. Wayne D. Blackmon, President, American Society of Psychoanalytic Physicians; Dr. Joseph D. Bloom, President, American Academy of Psychiatry and The Law; Dr. Shelia Blume, Past-President, American Society of Addiction Medicine; Dr. David W. Brook, Chairman, American Group Psychotherapy Association; Dr. Ewald W. Busse, Past-President, International Association of Gerontology; Dr. Robert B. Cahan, Representative, American Board of Forensic Psychiatry, Inc.; Dr. James M. Campbell, President, Philippine Psychiatrists of America; Dr. Doyle I. Carson, President, National Association of Private Psychiatric Hospitals; Dr. Pietro Castelnuovo-Tedesco, President, American College of Psychoanalysts; Dr. Gordon H. Clark, President, American Association of Community Psychiatrists; Reverend Victoria Brannan Cowell, President, Association of Mental Health Clergy; Dr. Joseph Czarsty, Chairman, American Academy of Family Physicians; Dr. Ezra C. Davidson, President, American College of Obstetricians and Gynecologists; Dr. Nicholas E. Davies, President-

Elect, American College of Physicians; Dr. K. Himasiri De Silva, President, Sri Lankan Psychiatrists in America; Dr. Darryl C. DeVivo, President, Child Neurology Society; Dr. Leah J. Dickstein, President, Association of Women Psychiatrists; Dr. Mina K. Dulcan, President, American Association of Directors of Psychiatric Residency Training, Inc.; Dr. D. Robert Fowler, President, National Association of VA Chiefs of Psychiatry; Ms. L. Patt Franciosi, President, National Mental Health Association; Dr. D. Ray Freebury, Past-President, Canadian Psychoanalytic Society; Dr. Desmond S. Fung, President, Association of Chinese American Psychiatrists; Dr. Patricia S. Goldman-Rakic, President, Society for Neuroscience; Mr. Gary Goldsmith, President, National Depressive and Manic Depressive Association; Dr. Frederick K. Goodwin, Administrator, Alcohol, Drug Abuse and Mental Health Administration; Dr. Enoch Gordis, Director, National Institute on Alcohol Abuse and Alcoholism; Dr. Stanley R. Graham, President, American Psychological Association; Dr. John Greden, President-Elect, Society of Biological Psychiatry; Dr. George T. Grossberg, President, American Association for Geriatric Psychiatry; Dr. Richard C.W. Hall, President, Academy of Psychosomatic Medicine; Dr. Katherine Halmi, President, American Psychopathological Association; Dr. Herndon P. Harding, Jr., Representative, National Association of State Mental Health Program Directors; Dr. Gaston P. Harnois, President, World Association for Psychosocial Rehabilitation; Dr. Thelissa A. Harris, President, Black Psychiatrists of America; Dr. Ali Jarrahi, President, Society of Iranian Psychiatrists in North America; Dr. Edward R. Kaufman, President, The American Academy of Psychiatrists in Alcoholism and Addictions; Ms. Constance E. Lieber, President, National Alliance for Research on Schizophrenia and Depression; Dr. Sidney Malitz, President, Benjamin Rush Society; Dr. Donald K. McRae, President, Canadian Psychiatric Association; Dr. Roger E. Meyer, President, American Association of Chairmen of Departments of Psychiatry; Dr. Robert M. Morse, President, Association for Medical Education and Research in Substance Abuse; Dr. Madeline Nagle, Representative, American Nurses' Association; Dr. Henry A. Nasrallah, President, American Academy of Clinical Psychiatrists; Dr. Romuald J. Orlowski, President, Association of Polish Psychiatrists and Neurologists in America; Ms. Venie Palasota, President, American Psychiatric Association Auxiliary; Dr. Elaine P. Pinderhughes, President, American Orthopsychiatric Association; Dr. Vivian W. Pinn-Wiggins, President, National Medical Association; Dr. Sr. Anna Polcino, Representative, National Guild of Catholic Psychiatrists; Mr. Thomas M. Posey, President, National Alliance for the Mentally Ill; Dr. Ghulam Qadir, President, Pakistan Psychiatric Society of America; Dr. Stephen L. Rachlin, President, American Association of Psychiatric Administrators; Dr. Carolyn B. Robinowitz, President, Group for the Advancement of Psychiatry; Dr. Robert Ruben, Representative, American Academy of Otolaryngology–Head & Neck Surgery; Dr. Richard M. Sarles, President, American Society for Adolescent Psychiatry; Dr. Stephen C. Scheiber, Executive Vice-President, American Board of Psychiatry and Neurology, Inc.; Dr. Jerald R. Schenken, Board of Trustees, American Medical Association; Dr. John E. Schowalter, President, American Academy of Child and Adolescent Psychiatry; Dr. Charles R. Schuster, Director, National Institute on Drug Abuse; Dr. Richard I. Shader, President, American College of Neuropsychopharmacology; Dr. G. Pirooz Sholevar, Representative, Society of Professors of

Child and Adolescent Psychiatry; Dr. Mahmoud S. Taman, President, Arab American Psychiatrists Association of America; Dr. Troy L. Thompson, President, Association for Academic Psychiatry; Dr. Jaime Trujillo, President, American Society of Hispanic Psychiatrists; Dr. Adnan Varol, President, Turkish-American Neuropsychiatric Association; Dr. Harold M. Visotsky, President, American Association for Social Psychiatry; Dr. Thomas N. Wise, President, American Association of General Hospital Psychiatrists; Dr. John C. Wolfe, President, American College of Mental Health Administration.

International Scholars: Dr. Timothy B. Crow of England; Dr. Johannes Meyer-Lindenberg of West Germany; Prof. Thomas R. Odhiambo of Kenya; Ambassador Shimon Shamir of Israel; and Prof. Toma Tomov of Bulgaria.

Representatives of Other International Organizations and Psychiatric Associations in Other Countries: Prof. Dr. Jorge Alberto Costa e Silva, World Psychiatric Association; Dr. Charles Thesiger, Caribbean Psychiatric Association; Dr. Irene Jakab, International Society on the Psychopathology of Expression; Dr. Osama Al Radi, World Islamic Mental Health Association; Prof. Dr. Edgar Heim, International Federation for Medical Psychotherapy; Dr. Eugene Brody, World Federation for Mental Health; Prof. Graham Burrows, Royal Australian and New Zealand College of Psychiatrists; Prof. Peter Berner, Austrian Society of Psychiatry and Neurology; Dr. Donald MacRae, Canadian Psychiatric Association; Dr. Yanping Zheng, Society of Psychiatry and Neurology of the People's Republic of China; Dr. Carlos Leon-Andrade, Ecuadorian Psychiatric Association; Prof. Ahmed Okasha, Egyptian Psychiatric Association; Dr. Kari Pylkkanen, Finnish Psychiatric Association; Dr. George Christodoulou, Hellenic Psychiatric Association; Dr. Cho-Man Chung, Hong Kong Psychiatric Association; Dr. Bela Buda, Hungarian Psychiatric Association; Dr. Tomas Zoega, Icelandic Psychiatric Association; Dr. Yomishi Kasahara, Japanese Society of Psychiatry and Neurology; Dr. Tetsuya Iwasaki, Japanese Psychoanalytic Association; Dr. Morihiro Sekiyama, Japanese Association of Psychiatric Hospitals; Dr. Chong Cheul Park, Korean Neuropsychiatric Association; Dr. Eli Karam, Lebanese Psychiatric Association; Dr. Lauro Castanedo, Mexican Psychiatric Association; Dr. Driss Moussaoui, Moroccan Society of Psychiatry; Prof. Dr. Willem Schudel, Netherlands Society for Psychiatry; Dr. Stein Opjordsmoen, Norwegian Psychiatric Association; Dr. Mohammed Chaudhry, Pakistan Psychiatric Society; Dr. Adnrzej Axer, Polish Psychiatric Association; Dr. Lee-Peng Kok, Singapore Psychiatric Association; Dr. James Birley, Royal College of Psychiatrists of the United Kingdom; Prof. Sydney Brandon, Psychiatric Section of the Royal Society of Medicine; Dr. Antonio Pacheco Hernandez, Venezuelan Psychiatric Association; Dr. Ruben Hernandez Serrano, Venezuelan Medical Federation; Dr. Abdelmagid Al-Khulaidi, Federation of Arab Psychiatrists and the Yemen Psychiatrists and Neurologists Association.

H. Keith H. Brodie, M.D., introduced Dr. Pardes, who gave the Presidential Address, "Defending Humanistic Values" (printed elsewhere in this issue of the *Journal*). Carol C. Nadelson, M.D., introduced Elissa P. Benedek, M.D., President-Elect of the Association, who gave the Response to the Presidential Address, "Our Children: Our Future" (printed elsewhere in this issue). Dr. Pardes then adjourned the Opening Session.

Business Meeting

The Annual Business Meeting was called to order by Herbert Pardes, M.D., in the Javits Convention Center on Monday, May 14, at 12:30 p.m.

First session. Bernice B. Elkin, M.D., Recorder, called the roll of the Assembly representatives and announced the presence of a quorum. Dr. Gerald H. Flamm, Speaker, spoke in tribute to Robert B. Neu, M.D. (1921–1990). Dr. Dale Cameron then spoke in tribute to Past President, Robert Felix, M.D. (1904–1990), after which Dr. Pardes asked the audience to observe a moment of silence in memory of all members and Fellows who died during the past year. Edward C. Kirby, Jr., M.D., chairperson of the Committee of Tellers, announced the results of the election of officers and Trustees. The reports to the membership followed. Philip M. Margolis, M.D., presented the Secretary's report, which was followed by the reports of

Alan I. Levenson, M.D., Treasurer; Gerald H. Flamm, M.D., Speaker of the Assembly; Edward Hanin, M.D., Speaker-Elect of the Assembly; Ralph A. O'Connell, M.D., chairperson of the Committee on the Constitution and By-Laws; and Michael J. Vergare, M.D., chairperson of the Membership Committee. Melvin Sabshin, M.D., presented the Medical Director's report. Reports of all the councils were also available. All reports were accepted by the membership as submitted and will be published in the October 1990 issue of the *American Journal of Psychiatry.*

Dr. John S. McIntyre presented the Speaker's plaque to Gerald H. Flamm, M.D., retiring Speaker, and Dr. Fred Gottlieb presented the Vice-President's badge to Lawrence Hartmann, M.D., retiring Vice-President. Dr. Paul J. Fink then presented the President's badge to Dr. Pardes. Dr. Pardes then recessed the first session of the business meeting.

Second Session. Following the business meeting Dr. Pardes called the Annual Forum, for all voting members, to order. The issues discussed on the floor included the industry sponsored symposia. A motion was made and seconded that a Task Force be established to review the implications of industry sponsored symposia and report its findings and recommendations to the Board of Trustees before the next Annual Meeting. However, a suggestion was made to refer the question to the Joint Reference Committee. This was acceptable to the maker of the original motion. The membership present then voted to refer the question of the implications of industry sponsored symposia to the Joint Reference Committee for reporting back within one year.

Another issue regarding the APA's involvement in Medicaid fraud enforcement was raised. The issue was discussed briefly, and it was noted that the issue of *Psychiatric News* immediately before the Annual Meeting featured a front page story on the issue, and that several groups within the APA were discussing ongoing problems in this arena. It was also mentioned that this issue would probably be on the Board of Trustee's June agenda.

The Annual Business Meeting and Forum were adjourned by Dr. Pardes at 2:00 p.m.

Convocation

The 34th Convocation of Fellows was held in the Javits Convention Center beginning at 8:00 p.m. on Monday, May 14. Dr. Pardes presided. After the processional march, Dr. Pardes called the Convocation to order. Dr. Pardes thanked Dr. Edward A. Siegel of San Diego, California, for playing the music during the processional. President-Elect Elissa P. Benedek, M.D., then led the ceremony conferring Life Fellowship and the induction of Fellows of the Association. Dr. Pardes read the names of the 1989 Corresponding Fellows: Jose Luis Ayuso-Gutierrez, M.D., Madrid, Spain; Joan M. Lawrence, M.D., Brisbane, Australia; Felice Lieh-Mak, M.D., Hong Kong; Juan J. Lopez-Ibor, Jr., M.D., Madrid, Spain; Miguel Angel Materazzi, M.D., Buenos Aires, Argentina; William Richard McLeod, M.D., Victoria, Australia; Johannes H. Meyer-Lindenberg, M.D., Bonn, West Germany; Robert G. Priest, M.D., London, England; Carlos Javier Ruiz-Ogara, M.D., Granada, Spain; William Joost Schudel, M.D., Den Haag, The Netherlands; and Marcio V. Versiani, M.D., Rio de Janeiro, Brazil. The following 50-Year Life Fellows and Life Members (1940–1990) were then recognized: Alexandra Adler, M.D., New York, NY; Leon L. Altman, M.D., New York, NY; Julius Barasch, M.D., Hollywood, FL; Helen B. Barton, M.D., Golden Valley, MN; Morris C. Beckwitt, M.D., Los Angeles, CA; Herman M. Brickhouse, M.D., Williamsport, PA; John E. Burch, M.D., Winnipeg, Canada; Anthony Karl Busch, M.D., Belleville, IL; Frank Cerulli, M.D., Rockville Centre, NY; C. Perry Cleaver, M.D., Catawissa, PA; Jules Victor Coleman, M.D., New Haven, CT; Ralph T. Collins, M.D., Hilton Head Island, SC; William H. English, M.D., Hollywood, FL; Malcolm H. Finley, M.D., Danville, CA; Arthur N. Fleiss, M.D., Syracuse, NY; Leonard C. Frank, M.D., Vista, CA; John Frosch, M.D., Great Neck, NY; Jules Gelperin, M.D., Lake Forest, IL; Elmer Haynes, M.D., Santa Barbara, CA; Alex H. Kaplan, M.D., St. Louis, MO; Charles J. Katz, M.D., Missoula, MT; Samuel R. Lehrman, M.D., Los Altos, CA; Murray D. Lewis, M.D., Sarasota, FL; Ruth W. Lidz, M.D., Wood-

bridge, CT; Joseph A. Luhan, M.D., St. Petersburg, FL; Oscar B. Markey, M.D., Cleveland, OH; Ben Marks, M.D., Detroit, MI; Joseph H. Marshall, M.D., Charleston, SC; Robert B. May, M.D., St. Cloud, MN; Dick C. McCool, M.D., Memphis, TN; Clementine C. McKeon, M.D., Manchester, CT; William K. McKnight, M.D., Green Valley, AZ; Holland C. Mitchell, M.D., Waco, TX; Robert J. Mueller, M.D., St. Louis, MO; Robert M. Newhouse, M.D., Long Beach, CA; John Goodman Novak, M.D., Lynchburg, VA; Rudolph G. Novick, M.D., Lincolnwood, IL; Douglass W. Orr, M.D., Santa Rosa, CA; Raymond Lester Osborne, M.D., Ft. Lee, NJ; L. Secord Palmer, M.D., Royal Palm Beach, FL; Albert Dixon Pattillo, M.D., Denton, TX; Saul K. Pollack, M.D., Milwaukee, WI; Morris D. Riemer, M.D., Hollywood, FL; Annemarie R. Rohan, M.D., Manteno, IL; Milton Rosenbaum, M.D., Augusta, KY; Robert B. Sampliner, M.D., Pasadena, CA; James S. Scarborough, M.D., Waco, TX; Nathan S. Schlezinger, M.D., Jenkintown, PA; Clarence M. Schrier, M.D., Kalamazoo, MI; Bruno G. Schutkeker, M.D., Buffalo, NY; Herman Selinsky, M.D., Miami, FL; Donald Shaskan, M.D., San Francisco, CA; Clifford H. Skitch, M.D., Vancouver, Canada; Robert J. Stein, M.D., Harlingen, TX; Ralph M. Stolzheise, M.D., Seattle, WA; Anthony S. Tagliavia, M.D., Hauppage, NY; B. Frank Vogel, M.D., Gulfport, MS; Philip S. Wagner, M.D., Alta Loma, CA; Guy M. Walters, M.D., Rochester, NY; Lloyd E. Watts, M.D., Camillus, NY; Carl A. Whitaker, M.D., Nashotah, WI; Murray A. Yost, M.D., Buffalo, NY; David A. Young, M.D., Raleigh, NC. Dr. Pardes then presented Mr. Ralph C. Kelzer with his Honorary Fellow medallion and certificate.

Special Presidential Commendations were presented to James P. Comer, M.D., "in appreciation of his excellent application of psychiatric principles and practice to empower schools and school children, and for his contributions to the prevention of childhood emotional disorders"; to Shelby Modell, "in appreciation of her enormous energy and foresight as an important proponent of the increased support of psychiatric research, as well as for her work to increase public and private funding for research in mental illness"; to James A. Kulikowski, J.D., "in appreciation of his leadership in public policy, and his dedication and commitment to the best interests of the nation's health and mental health"; to Michael A. Stephens, "in appreciation of his leadership in public policy, and his dedication and commitment to the best interests of the nation's health and mental health"; to Richard C. Surles, Ph.D., "in appreciation of his thoughtful and creative application of mental health policy to one of the largest mental health systems within the country"; and to Joseph Zubin, Ph.D., "in appreciation of his extraordinary leadership in fostering the biometric approach to research in mental illness."

Dr. Pardes introduced Senator Lowell Weicker, Jr., President and Chief Executive Officer of Research!America. Senator Weicker's political career began in 1962 when he won election to the Connecticut General Assembly, a seat to which he was reelected twice. He served concurrently as First Selectman of Greenwich from 1964 to 1968 and, in 1968, was elected United States Congressman from Connecticut's fourth district. He was subsequently elected to the United States Senate in 1970, 1976 and 1982. Senator Weicker gave the William C. Menninger Memorial Convocation Lecture, "Getting Your Jerseys Dirty."

After introducing the chairpersons of the award committees, Dr. Pardes presented the 1990 awards. Distinguished Service Awards were presented by Dr. Pardes to Daniel X. Freedman, M.D., Past President of the APA; to Gerald L. Klerman, M.D., professor and associate chairman for research in the department of psychiatry at Cornell University Medical College; and to the National Alliance for Research on Schizophrenia and Depression. This award was established by the Board of Trustees in 1964 to honor APA members who have contributed exceptional meritorious service to American psychiatry, and to organizations which have contributed greatly to the American Psychiatric Association and its work.

Stuart L. Keill, M.D., professor of psychiatry and vice-chairman for Clinical Affairs at the University of Maryland School of Medicine in Baltimore, and Medical Director of the Institute of Psychiatry and Human Behavior of the University of Maryland Medical System, received the Administrative Psychiatry Award. Established in 1983, this award honors an APA member who is a nationally recognized clinician executive, whose effectiveness as an administrator of major mental health programs has expanded the body of knowledge of management in the mental health services delivery system, and whose effectiveness has made it possible for them to function as a role model for other psychiatrists.

The APA/Dista Products Resident Research Award, established in 1988 to honor a psychiatry resident for excellence in research undertaken during residency, was presented to Aldo J. Castiglioni, Jr., M.D., a resident-in-training at the University of Texas Health Sciences Center at San Antonio, Texas; to Duncan B. Clark, M.D., a resident-in-training at Western Psychiatric Institute and Clinic; and to John Kasckow, M.D., a resident-in-training at Duke University Medical Center.

The first APA/Wisniewski Young Psychiatrist Research Award, established in 1989 in honor of the late Dr. Alexander A. Wisniewski, was presented to Eric Hollander, M.D., for his outstanding research activities conducted as a young psychiatrist.

Paul J. Fink, M.D., APA Past President, Chairman, department of psychiatry, Albert Einstein Medical Center, and medical director of the Philadelphia Psychiatric Center, received the Francis J. Braceland Award for Public Service. This award was established in 1977 to honor members of the Association who have made outstanding contributions as an author, spokesperson and advocate in the service of the mentally ill and disabled, and to the art and science of helping them.

The Foundations' Fund Prize for Research in Psychiatry, established to recognize outstanding research in psychiatry and its basic sciences, was awarded to John M. Kane, M.D., chairman of the department of psychiatry at the Hillside Hospital Division of Long Island Jewish Medical Center and professor of psychiatry at the Albert Einstein College of Medicine.

The Samuel G. Hibbs Award was presented to Mardi J. Horowitz, M.D., professor of psychiatry at the University of California, San Francisco. This award is given for the best unpublished paper on a clinical subject.

The Blanche F. Ittleson Award for Research in Child Psychiatry, given to a child psychiatrist or group of investigators for published results of research pertaining to the mental health of children, was presented to Edward R. Ritvo, M.D., professor in the division of Mental Retardation and Child Psychiatry, UCLA School of Medicine.

The Kempf Fund Awards for Research Development in Psychobiological Psychiatry were presented to Gustav Degreef, M.D., a staff psychiatrist on the Schizophrenia Clinical Service at Hillside Hospital and affiliated with NIMH Clinical Research Center for the Study of Schizophrenia, to honor a resident who demonstrates exceptional promise in psychiatric research; and to John M. Kane, M.D., chairman of the department of psychiatry at the Hillside Hospital Division of Long Island Jewish Medical Center and professor of psychiatry at the Albert Einstein College of Medicine, to honor research excellence in the psychobiological, psychological, and/or sociological causes and treatment for the mental disease known as schizophrenia.

Magda Campbell, M.D., professor of psychiatry at New York University Medical Center and director, division of Child and Adolescent Psychiatry, received the Agnes Purcell McGavin Award, given to honor a psychiatrist who has done and is currently doing outstanding work related to the preventive aspects of the emotional disorders of childhood, through framing concepts, developing proofs or creating applications.

The Robert T. Morse Writers Award, which honors popular writers who have made major contributions to the public understanding of psychiatry and mental illness, was presented to Mr. David Gelman, senior science writer for *Newsweek*, and to Ms. Erica E. Goode, associate editor for behavioral sciences at *U.S. News and World Report*.

Peter Gay, Ph.D., Sterling Professor of History at Yale University, received the Oskar Pfister Award, given to honor outstanding contributions in the field of psychiatry and religion.

The Psychiatric Institutes of America Foundation Award for Research Development in Hospital Psychiatry, given to honor outstanding contributions in hospital psychiatry research, was presented to Thomas H. McGlashan, M.D., director of research at

Chestnut Lodge Hospital and research professor of psychiatry at the University of Maryland School of Medicine.

Paul S. Appelbaum, M.D., Arnold Frank Zeleznik Distinguished Professor of Psychiatry and director, Law and Psychiatry Program, University of Massachusetts Medical Center, received the Isaac Ray Award, given to those who have made outstanding contributions to forensic psychiatry and to the psychiatric aspects of jurisprudence.

CBS News' "48 Hours," the single-topic, weekly news hour anchored by Dan Rather, received the Robert L. Robinson Award for its outstanding episode on schizophrenia, "Out of Mind." This award recognizes radio and television (including cable) productions that contribute significantly to a better public understanding of psychiatry and mental illness.

The Arnold L. van Ameringen Award in Psychiatric Rehabilitation was presented to Leonard I. Stein, M.D., professor of psychiatry at the University of Wisconsin Medical School in Madison, for his outstanding contribution to the field of psychiatric rehabilitation, in the areas of service, research, education, advocacy or a combination thereof.

The Seymour D. Vestermark Award, which recognizes an educator who has made outstanding contributions to undergraduate, graduate, or postgraduate education and career development in psychiatry, was presented to the American College of Neuropsychopharmacology, which was founded in 1961 as a professional organization of more than 500 leading scientists, who are selected primarily because of their contribution to original research in the field of neuropsychopharmacology.

The Jack Weinberg Memorial Award for Geriatric Psychiatry was presented to Charles E. Wells, M.D., clinical professor of psychiatry and neurology at Vanderbilt and director of a geriatric psychiatry unit at Parthenon Pavillion. This award honors a psychiatrist who has demonstrated special leadership or who has done outstanding work in clinical practice, training, or research into geriatric psychiatry anywhere in the world.

After the presentation of these awards, Dr. Pardes adjourned the Convocation.

Awards presented at meetings other than the Convocation included the following:

District Branch Newsletter of the Year Awards were presented to the *Pennsylvania Psychiatrist*, Denis Milke, M.D., Editor; *APS Action*, James F. Hooper IV, M.D., Editor; and the Five Year Award was presented to *The Washington Psychiatric Society Newsletter*, Judith Nowak, M.D., Editor.

The Manfred S. Guttmacher Award, given to honor outstanding contributions to the literature of forensic psychiatry, was given to Richard Rogers, Ph.D., senior psychologist and coordinator of research at METFORS, Clarke Institute of Psychiatry.

The Lilly Psychiatric Research Fellowship was awarded to Christopher J. McDougle, M.D., currently a resident in psychiatry at Yale University. The fellowship was established to provide support for the career development of a postgraduate medical trainee who has shown exceptional promise in psychiatric research.

The Jacob K. Javits Public Service Award, which honors a public servant who has made a significant contribution to the cause of the mentally ill, was received by Senator Kenneth C. Royall, Jr.

Scientific Sessions

The Scientific Program began on Monday, May 14, but continuing medical education (CME) courses and industry sponsored symposia began on Saturday, May 12. There were 21 discussion groups; five forums; 119 symposia; 24 industry sponsored symposia; two special Presidential symposia; 680 new research presentations; two debates; one new format, "round table discussion"; 163 papers presented in 54 paper sessions; 162 workshops (including 65 APA component presentations); 18 film sessions; 30 videotape sessions and two video production clinics; 106 CME courses; four medical updates; five review of psychiatry sessions; four clinical case conferences; two two-part continuous clinical case conferences; three "research consultations with . . . " sessions; and eight "clinical consultations with . . . " sessions. Other sessions included "Research Advances in Psychiatry: An Update for the Clinician"; "Workshops on Private

Practice Issues"; the residents' session, "Meet the Experts: Sunny-Side Up"; "Patients, Consumers, and Their Families"; the NIMH Workshop; the Public Symposium; the Social Security Workshop; and an AIDS Program and Resource Center.

There were 30 lectures presented. The speakers, their current positions, and the titles of their presentations are listed here.

On Monday, May 14, the following speakers gave lectures: Clarice J. Kestenbaum, M.D., Director of Training and Clinical Professor in the Division of Adolescent Psychiatry at Columbia University College of Physicians and Surgeons in New York, "Outcome of Children at Risk for Major Psychiatric Disorder: A Twenty-Year Follow-up"; Sander L. Gilman, Ph.D., Goldwin Smith Professor of Humane Studies and Professor of the History of Psychiatry at Cornell University, the APA's Benjamin Rush Lecture, "Seeing the Hysteric: Race and Gender in Fin-de-Siecle Psychiatry"; Frederick K. Goodwin, M.D., Administrator of the Alcohol, Drug Abuse, and Mental Health Administration, "The Frequent Association of Bipolar Illness and Substance Abuse: Causes and Consequences"; Robert Michels, M.D., Psychiatrist-in-Chief at New York Hospital, Payne Whitney Clinic and the Westchester Division, "Sex, Ethics and Psychotherapy"; Marie Balter, Founder of the Balter Institute and a former patient and social worker at Danvers State Hospital in Massachusetts, the APA's Patient Advocacy Lecture, "Vision of Hope"; Stuart L. Keill, M.D., Medical Director of the Institute of Psychiatry and Human Behavior of the University of Maryland Medical System, the APA's Administrative Psychiatry Lecture, "Strategies of Influence: The Psychiatrist Executive as Political Animal"; James P. Comer, M.D., Maurice Falk Professor of Child Psychiatry and Director of the School Development Program at the Child Study Center at Yale University, the APA's Solomon Carter Fuller Lecture, "Education and the American Future"; Timothy J. Crow, M.B., Head of the Division of Psychiatry and Deputy Director of the Clinical Research Centre at Northwick Park Hospital in Middlesex, England, "Brain Structure in Psychosis and the Decent of Man."

On Tuesday, May 15, the following lectures were given: Mardi J. Horowitz, M.D., Professor of Psychiatry at the University of California, San Francisco, and Director of the Program on Conscious and Unconscious Mental Processes of the John D. and Catherine T. MacArthur Foundation, the APA's Samuel G. Hibbs Lecture, "Conscious and Unconscious Mental Processes During Mourning"; June Jackson Christmas, M.D., Clinical Professor of Psychiatry at Columbia University College of Physicians and Surgeons, "Psychiatry and Public Policy: From Expendability to Equity"; Lewis L. Judd, M.D., Director of NIMH, "The Decade of the Brain (1990–2000): What It Will Mean to Psychiatry"; Gerald M. Edelman, M.D., Vincent Astor Professor and Director of the Neurosciences Institute at Rockefeller University in New York City, "Neural Darwinism: Population Thinking and Higher Brain Functions"; APA's Seymour D. Vestermark Presentation, made by the American College of Neuropsychopharmacology, Drs. Richard I. Shader, David S. Janowsky, Ira D. Glick, Carl Salzman, "The Teaching and Learning of Psychopharmacology in the 1990's: How to Jump on a Rapidly Moving Train"; Allen J. Frances, M.D., Professor of Psychiatry at Cornell University Medical College and Chairperson of the APA's Task Force on DSM-IV, "Conceptual Problems of Psychiatric Classification"; Professor Thomas R. Odhiambo, Director of the International Centre of Insect Physiology and Ecology in Nairobi, Kenya, "Locust Swarming: A Plague in Fact and Mind"; Tony Award winners Stephen Sondheim and James Lapine, "Creativity and Collaboration: A Conversation with Stephen Sondheim and James Lapine"; Professor Toma Tomov, Associate Professor and Head of the Outpatient Clinic in the Department of Psychiatry at the Medical College and Coordinator of the World Health Organization Collaborating Centre for Research and Training in Mental Health in Sofia, Bulgaria, "The Impact of Political Change in Eastern Europe on the Advancement of Behavioral Sciences and Psychiatry."

On Wednesday, May 16, the following lectures were presented: Arnold M. Ludwig, M.D., E.A. Edwards Professor of Psychiatry at the University of Kentucky College of Medicine, "Creativity and Aberration"; Herbert D. Kleber, M.D., Deputy Director for Demand Reduction at the Office of National Drug Control Policy, "The Role of Research, Prevention and Treatment in the National Drug Control Strategy"; Ambassador Shimon Shamir, Israeli Ambassador

to Egypt, "Mutual Perceptions and Historical Images in Conflict Resolution"; Gerald L. Klerman, M.D., Professor and Associate Chairman for Research in the Department of Psychiatry at Cornell University Medical College, APA's Adolf Meyer Lecture, "Science and Humanism in American Psychiatry: The Legend of Adolf Meyer"; Floyd E. Bloom, M.D., Chairman of the Department of Neuropharmacology at the Scripps Clinic and Research Foundation in La Jolla, California, "The Emerging Neuropharmacology of Alcohol"; Carter Heyward, Ph.D., Professor of Theology at the Episcopal Divinity School in Cambridge, Massachusetts, "Compassionate Re-Membering: Spirituality, Sanity and Morality in a Dismembered World"; Tom Wolfe, noted author, "Money Fever"; Johannes Meyer-Lindenberg, M.D., President of the German Society of Psychiatry and Nervous Diseases and Counseling Neuropsychiatrist at Protestant Hospital in Bonn, "The Effects of the Holocaust on German Psychiatry."

The lectures presented on Thursday, May 17, were the following: Mortimer Mishkin, Ph.D., Chief of the Laboratory of Neuropsychology at the National Institute of Mental Health, "Cerebral Memory Circuits"; Peter Gay, Ph.D., Sterling Professor of History at Yale University, "A Godless Jew Revisited"; and Paul Greengard, Ph.D., Professor of Molecular and Cellular Neuroscience at Rockefeller University in New York, "Neuronal Phosphoproteins: Mediators of Signal Transduction."

Other Activities

The Committee on Local Arrangements, Philip R. Muskin, M.D., chairperson, planned many activities, among which were a "fun run," golf and tennis tournaments, and birdwatching. Some of the tours included Dinner Cruise Around Manhattan, Statue of Liberty Excursion, New York Stock Exchange, Designer Shopping on Lower East Side, and a Lincoln Center Tour.

Meeting of the Board of Trustees

The Board of Trustees met in regular session on Sunday, May 13.

Meetings of the Assembly

The Assembly met on Friday, Saturday, and Sunday, May 11, 12, and 13.

PHILIP M. MARGOLIS, M.D.
Secretary, American Psychiatric Association

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The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY
Metabolism
The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.
Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.
Additional information on metabolism appears in Full Prescribing Information.

CONTRAINDICATIONS
Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.
The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS
1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**
   Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**
   Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS
1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS
Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.
Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and

"sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity (See WARNINGS, Use in Children.)
Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.
Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia; tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.
Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.
Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.
Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.
Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.
Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE
There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.
Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.
The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid base balance are well known in most medical centers and are not further discussed here.
Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.
The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.
Other possible therapeutic considerations include:
   (a) Dialysis: Desipramine is found in low concentration in the serum, even after massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.
   (b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levarterenol and metaraminol, they should be used with caution.
   (c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider parenteral use of diphenylhydantoin, which has less central depressant effect and also has an effect on heart rhythm that has not yet been fully defined.
   (d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

Product Information as of January, 1989

Y398

MERRELL DOW PHARMACEUTICALS INC.
Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

Information for Contributors

GENERAL POLICIES

The requirements stated below are in accordance with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

Prior Publication

Manuscripts are accepted for consideration by the *American Journal of Psychiatry* with the understanding that they represent original material, have not been published previously, are not being considered for publication elsewhere, and have been approved by each author. Any form of publication other than an abstract of no more than 400 words constitutes prior publication. This includes components of symposia, proceedings, transactions, books (or chapters), articles published by invitation, or reports of any kind, regardless of differences in readership, as well as electronic data bases of public nature. Authors submitting manuscripts containing data or clinical observations already used in published papers or used in papers that are in press, submitted for publication, or to be submitted shortly should provide this information and copies of those papers to the Editor. An explanation of the differences between the papers should be included.

Copyright Transfer and Submission Approval

The *Journal* requires approval of manuscript submission by all authors in addition to transfer of copyright to the American Psychiatric Association so that the author(s) and the Association are protected from misuse of copyrighted material. A submission approval and copyright transfer form will be forwarded to authors along with a letter acknowledging receipt of their manuscript. Manuscripts will not receive a final decision until a completed form has been received in the editorial office.

In addition, authors must obtain letters of permission from publishers for use of extensive quotations (more than 500 words). The *Journal* does not publish tables or figures that have been previously published or submitted elsewhere.

Disclosure of Commercial Interests

All forms of support, including drug company support, must be acknowledged in the author's footnote (see "Acknowledgments" under the Title Page section). Also, authors must disclose in their cover letter any commercial or financial involvements that might present an appearance of a conflict of interest in connection with the submitted article, including but not limited to institutional or corporate affiliations not already specified in the author's footnote, paid consultancies, stock ownership or other equity interests, and patent own-

ership. At the Editor's discretion, this information may be shared with reviewers. Such involvements will not be grounds for automatic rejection of the manuscript. Should the article be accepted for publication, the Editor and the authors will consult on whether, and to what extent, this information should be included in the published article.

Patient Anonymity

Ethical as well as legal considerations require careful attention to the protection of a patient's anonymity in case reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. In addition, authors should disguise identifying information when discussing the characteristics and personal history of patients.

Informed Consent

Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children, authors are asked to include information about whether the child's assent was obtained.

Review Process

All papers are reviewed to determine the originality, validity, and importance of content and conclusions. In addition to the regular review process, peer review for statistical content may be required for some manuscripts. This will be determined by the *Journal's* Statistical Editors. Authors will be sent reviewer comments that are judged to be useful to them. All reviewers remain anonymous. Once the Editor has made a final decision on a paper, the authors of that paper will be informed.

SUBMISSION OF MANUSCRIPTS

The original manuscript and four copies should be submitted to John C. Nemiah, M.D., Editor, *American Journal of Psychiatry*, 1400 K St., N.W., Washington, DC 20005. All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the *Journal* it is being submitted (i.e., Special Article, Regular Article, or Clinical and Research Report); papers will only be reviewed after such a statement has been received from the author.

Authors will be notified of the receipt of their paper and

the number assigned to it. **This number must be included in all further correspondence.** It is imperative that the corresponding author of submitted papers notify the *Journal* of changes of address. Because of escalating postage costs, no manuscripts submitted to the *Journal* will be returned to authors except upon special request. Authors must make this request in their original submission letter and include a self-addressed, postage-paid envelope.

Single Case Reports

Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All single case reports will be peer reviewed. Reports of successfully treated patients must include data on the number of patients treated unsuccessfully by the same method, with an indication of the temporal order of the successes and failures.

Annual Meeting Papers

Authors may submit their papers before the annual meeting, but such papers cannot be published until after the meeting. All papers must be accompanied by a statement that they are in final form. These papers are subject to the same peer review as other papers and must conform to the requirements for one of the types of articles specified in the next section.

TYPES OF ARTICLES

Special Articles

These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including an abstract of no more than 100 words, tables, and figures) and may not include more than 100 references.

Regular Articles

Regular Articles are original communications of scientific excellence in psychiatric medicine and advances in clinical research. Regular Articles contain no more than 3,800 words, including an abstract of no more than 100 words, references, tables, and figures. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. Articles that exceed 3,800 words will be returned unreviewed to the authors.

Clinical and Research Reports

Clinical and Research Reports may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a **maximum** of 1,300 words, including an abstract of no more than 40 words, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile

replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

Other Sections

Letters to the Editor. Brief letters (maximum of 500 words and 5 references; no tables or figures) will be considered if they include the notation "for publication." Letters critical of an article published in the *Journal* will automatically be sent to the authors for reply. Because of space limitations not all letters can be printed. The *Journal* will notify authors about the disposition of their letters but does not return those that are not published. A letter must be signed by all of its authors. All letters will be edited; edited letters will not be sent to authors for approval. Letters must be typed **double-spaced** throughout on 8½×11 inch paper; three copies are required. Letters that do not meet these specifications will be returned for revision. Reprints are not available. **Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. Case reports submitted as Letters to the Editor will be peer reviewed.**

Book Forum. Books for review may be sent to the Book Forum Editor, Nancy C. Andreasen, M.D., Ph.D., University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242. Book reviews are usually solicited by the Book Forum Editor. Authors interested in reviewing a particular book should communicate directly with Dr. Andreasen. Reprints of reviews are not available.

TYPING AND ARRANGING THE PAPER

All parts of the manuscript, including case reports, quotations, references, and tables, must be **double-spaced** throughout. Manuscripts must be typed in upper- and lowercase on one side only of 8½×11 inch **nonerasable** bond paper. All four margins must be 1½ inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered.

STYLE SPECIFICATIONS

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Title. The title should be informative and as brief as possible. Two-part titles should be avoided.

By-line. Authors listed in the by-line should be limited to principal researchers and/or writers; collaborators may be acknowledged in a footnote. Authors' first names are preferred to initials. Degrees should be included after each author's name.

Previous presentation. If the paper has been presented at a meeting, please give the name of the meeting, the place, and the date.

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Acknowledgments. Grant support should be acknowledged in a separate paragraph and should include the full

name of the granting agency and grant number. The *Journal* does not allow acknowledgment of persons involved with the preparation or typing of manuscripts. Acknowledgment of individuals involved with the scientific content of the work should not exceed four typed lines. Drug company support of any kind must be acknowledged.

Abstract

The abstract is a single paragraph no longer than 100 words for Special Articles and Regular Articles and no longer than 40 words for Clinical and Research Reports.

Text

Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

Research design and statistics. The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. **All** significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3$, 17, $p< 0.05$)." Reviewers will evaluate the appropriateness of the analyses.

Abbreviations. Spell out all abbreviations (other than those for units of measure) the first time they are used. Idiosyncratic abbreviations should not be used.

Drugs. Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

References

References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. Do **not** arrange the list alphabetically. References in tables and figures are numbered as though the tables and figures were part of the text.

References should be restricted to closely pertinent material. **Accuracy of citation is the author's responsibility.** References should conform exactly to the original spelling, accents, punctuation, etc. Authors should be sure that all references listed have been cited in text.

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Type references in the style shown below, **double-spaced throughout.** List up to three authors; designate one or more authors past the third as "et al." Abbreviations of journal names should conform to the style used in *Index Medicus*; journals not indexed there should not be abbreviated.

1. Noyes R Jr, DuPont RL Jr, Pecknold JC, et al: Alprazolam in panic disorder and agoraphobia, results from a multicenter trial, II: patient acceptance, side effects, and safety. Arch Gen Psychiatry 1988; 45:423–428
2. Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987

TABLES AND FIGURES

The *Journal* does not publish tables or figures that have been submitted elsewhere or previously published. Tables and figures that duplicate 1) material contained in text or 2) each other will not be used. Authors will be asked to delete tables and figures that contain data which could be given succinctly in text. Each table and figure should be understandable without reference to the text; a descriptive, concise title should be included and units of measurement should be specified. Consult recent issues of the *Journal* for format. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. **A copy of each table and figure must be included with each copy of the manuscript.**

Tables

Tables should be double-spaced, no wider than 120 typewriter characters, including spaces, and no longer than 70 lines. Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given.

Figures

Figures are considered as text and are subject to revision by the authors upon recommendation of the Editors. Figures should, however, be professionally prepared. Glossy or other camera-ready prints should accompany the submitted manuscript. Computer-generated figures that do not meet quality printing standards will be returned for revision. The first author's name, the title of the paper, the figure number, and the top of the figure should be noted on a label affixed to the back of each figure. All figure titles and footnotes should be typed and sent together on a separate page.

The *Journal* does publish color illustrations. However, the cost to publish them, including reprint charges, will be the responsibility of the authors. An estimate of the cost will be provided to the authors at the time of first decision.

Format. Figures are visual expressions of data trends or relationships. Figures that represent numerical data which could be expressed more succinctly or clearly in tabular form should be converted to tables. Line graphs should show change in continuous variables; comparisons of like values in different groups should be presented as bar graphs. Graphs containing stacked bars are unacceptable; the different segments of each bar should be presented side by side.

Lettering. Figure type should be sans serif and should be 7 points or larger after the figure is reduced; most figures taking up the width of a vertical manuscript page are reduced to a width of 19.5 picas (3¼ inches), and those requiring a horizontal manuscript page are usually reduced to 40.5 picas (6¾ inches). When space on the horizontal axis is insuffi-

FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects

[a]Significant difference between men and women (t=1.81, df=10, p<0.05) and between the total Alzheimer's disease group and the total control group (t=2.49, df=25, p<0.01).
[b]Significant difference between the total depressed group and the total control group (t=2.75, df=33, p<0.005).

cient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

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1. Do not use solid black shading; rather, include outlined white among shadings.

2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.

3. Error bars should not be used.

4. Do not extend the vertical or horizontal axis of a graph beyond the point needed for the data shown.

5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.

6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.

7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).

8. The key should appear within or above the figure but should not be wider than the figure itself. Avoid placing other type (e.g., number of subjects, statistical values) within the axes of a graph.

9. Footnotes (including p values) should be cited with superscript letters in the title or body of the figure and should be listed in the order in which they are cited in the figure.

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ORAP™ (pimozide) Tablets
The Less Sedating Therapy for Tourette Syndrome

INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment for tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

1. ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than associated with Tourette's Disorder.
2. ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., pemoline, methylphenidate and amphetamines) until such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
3. Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
4. ORAP is contraindicated in patients with severe toxic central nervous system depression or comatose states from any cause.
5. ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following: (see also PRECAUTIONS–Information for Patients).

Tardive Dyskinesia A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has under the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS–Information for Patients.)

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a tumorigenic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS–Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

Laboratory Tests An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QT_c interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency, secondary to diuretics, diarrhea, or other cause, should be corrected before ORAP therapy is initiated and normal potassium maintained during therapy.

Drug Interactions Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about fifteen times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known.

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

Pregnancy Category C Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks.

Labor and Delivery This drug has no recognized use in labor or delivery.

Nursing Mothers It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

ADVERSE REACTIONS

General: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported frequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under 'Tardive Dyskinesia' except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes: Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizure have occurred at doses above 20 mg/day

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS.)

Hyperpyrexia: Hyperpyrexia has been reported with other antipsychotic drugs.

Clinical Trials The following adverse reaction tabulation was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Diarrhea	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Eructations	0	1
Thirsty	1	0
Appetite increase	1	0

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Stooped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	1
Akathisia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Akinesia	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior effect	5	0
Special Sense		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes to light	1	0
Decreased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigational experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

Other Adverse Reactions In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema

Cardiovascular/Respiratory: Postural hypotension, hypotension, hypertension, tachycardia, palpitations

Gastrointestinal: Increased salivation, nausea, vomiting, anorexia, GI distress

Endocrine: Loss of libido

Metabolic/Nutritional: Weight gain, weight loss

Central Nervous System: Dizziness, tremor, parkinsonism, fainting, dyskinesia

Psychiatric: Excitement

Skin: Rash, sweating, skin irritation

Special Senses: Blurred vision, cataracts

Urogenital: Nocturia, urinary frequency

Postmarketing Reports The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ORAP.

Hematologic: Hemolytic anemia

OVERDOSAGE

In general, the signs and symptoms of overdosage with ORAP (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdosage, gastric lavage, establishment of a patent airway and, if necessary mechanically-assisted respiration are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose.

DOSAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on tic manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief afforded is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS–Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of ORAP, consideration should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal related phenomenon rather than a return of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

HOW SUPPLIED

ORAP (pimozide) 2 mg tablets, white, scored, imprint "LEMMON" and "ORAP-2"—NDC 57844-187-01, bottles of 100.

Dispense in tight, light-resistant containers as defined in the official compendium.

Made in Canada

GATE Pharmaceuticals
Division of Lemmon Company

1. Shapiro AK et al: *Pediatrics* 79:1032-1038, 1987.
2. Ross MS et al: *Am J Psychiatry* 135:585-587, 1978.

PR�ZAC®
fluoxetine hydrochloride

The antidepressant most frequently prescribed by psychiatrists in the United States[1]

Prozac® (fluoxetine hydrochloride)

Brief Summary.
Consult the package insert for complete information.

Indications: For the treatment of depression.

Contraindication: Known hypersensitivity to Prozac.

Warnings: *Monoamine Oxidase Inhibitors* — The combined use of fluoxetine and MAO inhibitors should be avoided. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of an MAOI. Serious events, including death, have been reported to occur following the initiation of an MAOI shortly after discontinuation of fluoxetine.

Rash and Possibly Allergic Events — Approximately 4% of 5,600 fluoxetine patients developed a rash and/or urticaria in premarketing testing. Almost a third of these discontinued therapy because of rash and/or associated systemic signs or symptoms. Reported in association with rash were fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly upon discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all were reported to recover completely.

Of two patients who developed a serious cutaneous systemic illness during premarketing clinical trials, one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events possibly related to vasculitis have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or represent immunologic responses is not known. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

Precautions: *General* — Anxiety, Nervousness, and Insomnia — Reported by 10% to 15% of patients, 5% of whom discontinued fluoxetine.

Altered Appetite and Weight — Significant weight loss, especially in underweight patients, may be an undesirable result of treatment.

Approximately 9% of fluoxetine patients experienced anorexia in controlled clinical trials, an incidence approximately sixfold that seen with placebo. A weight loss >5% of body weight occurred in 13% of fluoxetine patients compared with 4% in those on placebo and 3% in those on tricyclics. However, only rarely did fluoxetine patients discontinue treatment because of weight loss.

Activation of Mania/Hypomania — Hypomania or mania occurred in approximately 1% of fluoxetine patients in premarketing testing.

Seizures — Twelve of 6,000 patients (0.2%) experienced convulsions (or, possibly, seizures). Prozac should be introduced with care in patients with a history of seizures.

Suicide — Close supervision of high-risk patients should accompany initial therapy. Prescriptions of Prozac should be written for the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites — Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment.

Use in Patients with Concomitant Illness — Caution is advisable in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. ECGs of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis, the clearances of fluoxetine and its active metabolite were decreased. A lower or less frequent dose should be used in patients with cirrhosis.

Fluoxetine should be used with caution in patients with severe renal impairment. In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation. Insulin and/or oral hypoglycemic dosage may need to be adjusted when fluoxetine therapy is instituted or discontinued.

Interference with Cognitive and Motor Performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug does not affect them adversely.

Information for Patients — Physicians should advise their patients to notify them if they:
• are taking or plan to take any prescription or over-the-counter drugs or alcohol
• become pregnant or intend to become pregnant during therapy
• are breast feeding an infant
• develop a rash or hives

Drug Interactions — Tryptophan — Five patients receiving tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors — See Warnings.

Other Antidepressants — There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents.

Lithium — There have been reports of both increased and decreased lithium levels and lithium toxicity. Lithium levels should be monitored.

Diazepam Clearance — The half-life of diazepam may be prolonged in some patients.

Drugs Tightly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma protein, the concurrent administration of fluoxetine and another tightly bound drug may cause a shift in plasma concentrations potentially resulting in an adverse effect. Adverse effects may also result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs — Caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy — There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility — There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at doses approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively revealed no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies in rats at doses approximately five and nine times the maximum human dose (80 mg) respectively revealed no adverse effects on fertility. A slight decrease in neonatal survival was noted, probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy — Teratogenic Effects — Pregnancy Category B — Reproduction studies in rats and rabbits at doses nine and 11 times the maximum human dose (80 mg) respectively revealed no evidence of harm to the fetus. Although there have been no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery — The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers — Because Prozac is known to be excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children — Safety and effectiveness in children have not been established.

Usage in the Elderly — In clinical studies of several hundred elderly patients, no unusual adverse age-related phenomena were identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients with concomitant systemic illnesses or those receiving concomitant drugs.

Hyponatremia — Hyponatremia (some cases with serum Na <110 mmol/L) has been reported, which appeared to be reversible on drug discontinuation. Some cases were possibly due to SIADH, and the majority have been in older patients and those taking diuretics or otherwise volume depleted.

Platelet Function — There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

Adverse Reactions: *Commonly Observed* — Nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment — Fifteen percent of 4,000 clinical trial patients discontinued fluoxetine due to an adverse event. The more common events included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials — The accompanying table enumerates adverse events that occurred at a frequency of ≥ 1% in controlled trials.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/Adverse Event*	Percentage of Patients Reporting Event Prozac (N = 1,730)	Placebo (N = 799)	Body System/Adverse Event*	Percentage of Patients Reporting Event Prozac (N=1,730)	Placebo (N=799)
Nervous			**Body as a Whole**		
Headache	20.3	15.5	Asthenia	4.4	1.9
Nervousness	14.9	8.5	Infection, viral	3.4	3.1
Insomnia	13.8	7.1	Pain, limb	1.6	1.1
Drowsiness	11.6	6.3	Fever	1.4	—
Anxiety	9.4	5.5	Pain, chest	1.3	1.1
Tremor	7.9	2.4	Allergy	1.2	1.1
Dizziness	5.7	3.3	Influenza	1.2	1.5
Fatigue	4.2	1.1	**Respiratory**		
Sedated	1.9	1.3	Upper respiratory		
Sensation disturbance	1.7	2.0	infection	7.6	6.0
Libido,			Flu-like		
decreased	1.6	—	syndrome	2.8	1.9
Light-headedness	1.6	—	Pharyngitis	2.7	1.3
Concentration,			Nasal congestion	2.6	2.3
decreased	1.5	—	Headache, sinus	2.3	1.8
Digestive			Sinusitis	2.1	2.0
Nausea	21.1	10.1	Cough	1.6	1.6
Diarrhea	12.3	7.0	Dyspnea	1.4	—
Mouth dryness	9.5	6.0	**Cardiovascular**		
Anorexia	8.7	1.5	Hot flushes	1.8	1.0
Dyspepsia	6.4	4.3	Palpitations	1.3	1.4
Constipation	4.5	3.3	**Musculoskeletal**		
Pain, abdominal	3.4	2.9	Pain, back	2.0	2.4
Vomiting	2.4	1.3	Pain, joint	1.2	1.1
Taste change	1.8	—	Pain, muscle	1.2	1.0
Flatulence	1.6	1.1	**Urogenital**		
Gastroenteritis	1.0	1.4	Menstruation, painful	1.9	1.4
Skin and Appendages			Sexual dysfunction	1.9	—
Sweating, excessive	8.4	3.8	Frequent micturition	1.6	—
Rash	2.7	1.8	Urinary tract infection	1.2	—
Pruritus	2.4	1.4	**Special Senses**		
			Vision disturbance	2.8	1.8

*Events reported by ≥1% of fluoxetine patients are included.
— Incidence <1%

Other Events Observed During Premarketing Evaluation in 5,600 Fluoxetine Patients — Frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole — Frequent: chills; Infrequent: chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; Rare: abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System — Infrequent: angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; Rare: AV block first-degree, bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System — Frequent: increased appetite; Infrequent: aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, thirst; Rare: bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System — Infrequent: hypothyroidism; Rare: goiter and hyperthyroidism.

Hemic and Lymphatic System — Infrequent: anemia and lymphadenopathy; Rare: bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional — Frequent: weight loss; Infrequent: generalized edema, hypoglycemia, peripheral edema, and weight gain; Rare: dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System — Infrequent: arthritis, bone pain, bursitis, tenosynovitis, and twitching; Rare: bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System — Frequent: abnormal dreams and agitation; Infrequent: abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; Rare: abnormal electro-encephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System — Frequent: bronchitis, rhinitis, and yawn; Infrequent: asthma, epistaxis, hiccup, hyperventilation, and pneumonia; Rare: apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages — Infrequent: acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; Rare: eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses — Infrequent: amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; Rare: blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System — Infrequent: abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; Rare: abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports — Voluntary reports of adverse events temporarily associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: cerebral vascular accident, confusion, dyskinesia, ecchymoses, gastrointestinal hemorrhage, hyperprolactinemia, pancreatitis, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, and violent behaviors.

Overdosage: *Human Experience* — As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. A second death involved fluoxetine, codeine, and temazepam.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment. The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

A single death attributed to overdose of fluoxetine alone has been reported.

PV 2478 DPP   [052490]

Additional information available to the profession upon request.

Prozac® (fluoxetine hydrochloride, Dista)

Prozac® (fluoxetine hydrochloride, Dista)

Prozac® (fluoxetine hydrochloride, Dista)

THORAZINE®
brand of
chlorpromazine

See complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Contraindications: Comatose states or presence of large amounts of C.N.S. depressants.

Warnings: The possibility of extrapyramidal reactions from chlorpromazine may confuse the diagnosis of Reye's syndrome or other encephalopathy. Therefore, avoid use in children or adolescents with suspected Reye's syndrome.

May cause persistent tardive dyskinesia, which appears to be irreversible in some patients. Reserve chronic neuroleptic treatment for patients with chronic illness 1) that is known to respond to neuroleptics and 2) for whom there are no safer but equally effective treatment options. Use the smallest effective dose over the shortest treatment duration. If signs and symptoms of tardive dyskinesia develop, consider discontinuing the neuroleptic. A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. To manage NMS 1) discontinue immediately antipsychotic drugs and any other drugs not essential to concurrent therapy; 2) treat symptoms intensively and monitor; 3) where possible, treat serious concomitant medical problems. If antipsychotic treatment is needed after recovery from NMS, consider reintroducing drug therapy and monitor the patient carefully as recurrences of NMS have been reported. 'Thorazine' ampuls and vials contain sodium bisulfite and sodium sulfite; the sulfite may cause allergic reactions, including anaphylactic symptoms. In patients with bone marrow depression or previously demonstrated hypersensitivity (e.g., blood dyscrasias, jaundice) with phenothiazines, do not administer 'Thorazine' unless the potential treatment benefits outweigh the possible hazards. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days therapy. Avoid concomitant use with alcohol. May counteract antihypertensive effect of guanethidine and related compounds. Use in pregnancy only when essential. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborns whose mothers had received chlorpromazine. Chlorpromazine is excreted in the breast milk of nursing mothers.

Precautions: Advise patients and/or guardians of the risk of tardive dyskinesia from chronic therapy. Use cautiously in persons with cardiovascular, liver, renal or chronic respiratory disease, or with acute respiratory infections. Patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the C.N.S. effects of chlorpromazine. Due to cough reflex suppression, aspiration of vomitus is possible. May prolong or intensify the action of C.N.S. depressants, organophosphorus insecticides, heat, atropine and related drugs. (Reduce dosage of concomitant C.N.S. depressants.) Anticonvulsant action of barbiturates is not intensified.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in glaucoma patients. May diminish the effect of oral anticoagulants, produce α-adrenergic blockade, and lower the convulsive threshold; dosage adjustment of anticonvulsants may be required. May interfere with Dilantin®* metabolism, causing 'Dilantin' toxicity. May cause false positive phenylketonuria test results. Do not use with Amipaque®†. Discontinue 'Thorazine' at least 48 hours before myelography, do not resume for at least 24 hours postprocedure, and do not use to control N/V prior to myelography or postprocedure with 'Amipaque'. Evaluate patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics periodically to decide whether the dosage could be reduced or therapy discontinued. Antiemetic effect may mask signs of overdosage of other drugs or obscure diagnosis and treatment of conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see Warnings). When used concomitantly, may obscure vomiting as a sign of toxicity of a cancer chemotherapeutic agent. Discontinue high-dose, long-term therapy gradually. Patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics should be evaluated periodically for possible adjustment or discontinuance of drug therapy.

Adverse Reactions: Drowsiness; cholestatic jaundice; agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura and pancytopenia; postural hypotension, tachycardia, fainting, dizziness and occasionally a shock-like condition; reversal of epinephrine effects; EKG changes have been reported; neuromuscular (extrapyramidal) reactions: dystonias, motor restlessness, pseudo-parkinsonism, persistent tardive dyskinesia, psychotic symptoms, catatonic-like states, cerebral edema; convulsive seizures; abnormality of the cerebrospinal fluid proteins; urticarial reactions and photosensitivity, exfoliative dermatitis, contact dermatitis; asthma, laryngeal edema, angioneurotic edema, and anaphylactoid reactions; lactation and breast engorgement (in females on large doses), false positive pregnancy tests, amenorrhea, gynecomastia; hyperglycemia, hypoglycemia, glycosuria; dry mouth, nasal congestion, constipation, adynamic ileus, urinary retention, priapism, miosis, mydriasis; after prolonged substantial doses, skin pigmentation, epithelial keratopathy, lenticular and corneal deposits and pigmentary retinopathy, visual impairment; mild fever (after large I.M. doses); hyperpyrexia; increased appetite and weight; a systemic lupus erythematosus-like syndrome; peripheral edema.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported but no causal relationship has been established.

How Supplied: Tablets: 10 mg, 25 mg or 50 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 100 mg and 200 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only).

Spansule® brand of sustained release capsules: 30 mg, 75 mg, 150 mg or 200 mg, in bottles of 50 and 500; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 300 mg, in bottles of 50; in Single Unit Packages of 100 (intended for institutional use only).

Ampuls: 1 mL and 2 mL (25 mg/mL), in boxes of 10, 100 and 500.

Multiple-dose Vials: 10 mL (25 mg/mL), in boxes of 1, 20 and 100.

Syrup: 10 mg/5 mL in 4 fl oz bottles.

Suppositories: 25 mg or 100 mg, in boxes of 12.

Concentrate: Intended for institutional use. 30 mg/mL, in 4 fl oz bottles and in cartons of 36 bottles. 100 mg/mL, in 8 fl oz bottles, in cartons of 12.

*phenytoin, Parke-Davis.
†metrizamide, Winthrop Pharmaceuticals.

Date of issuance June 1989
BRS-TZ:L73

SK&F Smith Kline &French Laboratories
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PHILADELPHIA, PA 19101

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Where is the Library and Archives?

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What's in the Archives?

The Archives holds the records created by the APA, such as minutes, reports, correspondence, and photographs. There are a few collections of papers of individual psychiatrists such as Daniel Blain, Leo Kanner and John C. Whitehorn. Additionally, the Archives is the sole repository for the papers of Albert Deutch. There are tapes and transcripts from an oral history project, and a collection of artifacts and photographs that relate to the history of American psychiatry. These materials may be used in the Archives or photocopied, but they do not circulate.

Does the Library have a rare book collection?

Yes. Our rare book collection contains many valuable and first editions of early works that reflect the history of psychiatry. Among its volumes are first edition copies of Benjamin Rush's *Medical Inquiries and Observations Upon the Diseases of the Mind* and Joseph Breuer and Sigmund Freud's *Studien uber Hysterie*.

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▓▓: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

▓esyrel® Dividose®

▓zodone HCl)

▓ON

▓(trazodone hydrochloride) is an antidepressant chemically unrelated to tricyclic, ▓or other known antidepressant agents. It is a triazolopyridine derivative designated 3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one hydro-▓SYREL is a white odorless crystalline powder which is freely soluble in water. Its ▓weight is 408.3. The empirical formula is $C_{19}H_{22}ClN_5O \bullet HCl$ and the structural ▓epresented as follows:

$$\text{N=}\ \text{N}\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—N}\qquad\text{N}\qquad\qquad\text{HCl}$$
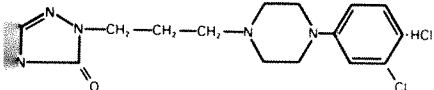
supplied for oral administration in 50 mg, 100 mg, 150 mg and 300 mg tablets.

▓ablets, 50 mg, contain the following inactive ingredients: dibasic calcium phos-▓ar oil, microcrystalline cellulose, ethylcellulose, FD&C Yellow No. 6 (aluminum lake), ▓gnesium stearate, povidone, sodium starch glycolate, and starch (corn).

▓ablets, 100 mg, contain the following inactive ingredients: dibasic calcium phos-▓ar oil, microcrystalline cellulose, ethylcellulose, lactose, magnesium stearate, povi-▓im starch glycolate, and starch (corn).

▓ablets, 150 mg, contain the following inactive ingredients: microcrystalline cellu-Yellow No. 6 (aluminum lake), magnesium stearate, pregelatinized starch, and

▓ablets, 300 mg, contain the following inactive ingredients: microcrystalline cellu-ferric oxide, magnesium stearate, sodium starch glycolate, pregelatinized starch, acid.

▓HARMACOLOGY

▓ism of DESYREL's antidepressant action in man is not fully understood. In animals, ▓electively inhibits serotonin uptake by brain synaptosomes and potentiates the ▓hanges induced by the serotonin precursor, 5-hydroxytryptophan. Cardiac conduc-of DESYREL in the anesthetized dog are qualitatively similar and quantitatively ▓nced than those seen with tricyclic antidepressants. DESYREL is not a monoamine ▓bitor and, unlike amphetamine-type drugs, does not stimulate the central nervous

▓SYREL is well absorbed after oral administration without selective localization in any ▓n DESYREL is taken shortly after ingestion of food, there may be an increase in the ▓rug absorbed, a decrease in maximum concentration and a lengthening in the time ▓m concentration. Peak plasma levels occur approximately one hour after dosing ▓REL is taken on an empty stomach or two hours after dosing when taken with food. of DESYREL is biphasic, consisting of an initial phase (half-life 3-6 hours) followed phase (half-life 5-9 hours), and is unaffected by the presence or absence of food. ▓learance of DESYREL from the body is sufficiently variable, in some patients ▓may accumulate in the plasma.

▓atients who responded to DESYREL, one-third of the inpatients and one-half of the had a significant therapeutic response by the end of the first week of treatment. ▓hs of all responders demonstrated a significant therapeutic effect by the end of the ▓ek. One-fourth of responders required 2-4 weeks for a significant therapeutic re-

▓NS AND USAGE

▓s indicated for the treatment of depression. The efficacy of DESYREL has been ▓ed in both inpatient and outpatient settings and for depressed patients with and ▓minent anxiety. The depressive illness of patients studied corresponds to the Major ▓Episode criteria of the American Psychiatric Association's Diagnostic and Statistical ▓a

▓essive Episode implies a prominent and relatively persistent (nearly every day for at ▓weeks) depressed or dysphoric mood that usually interferes with daily functioning, ▓s at least four of the following eight symptoms: change in appetite, change in sleep, ▓or agitation or retardation, loss of interest in usual activities or decrease in sexual ▓ased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired ▓on, and suicidal ideation or attempts.

▓DICATIONS

▓s contraindicated in patients hypersensitive to DESYREL.

▓S

▓E HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF PRIAPISM. IN APPROXI-▓3 OF THE CASES REPORTED, SURGICAL INTERVENTION WAS REQUIRED AND, IN A ▓OF THESE CASES, PERMANENT IMPAIRMENT OF ERECTILE FUNCTION OR IMPO-▓SULTED. MALE PATIENTS WITH PROLONGED OR INAPPROPRIATE ERECTIONS ▓MMEDIATELY DISCONTINUE THE DRUG AND CONSULT THEIR PHYSICIAN.

▓on should persist, promptly contact Bristol-Myers USPG Medical Services Depart-▓429-5591 or 812/429-5000).

▓escence of priapism and drug-induced penile erections by the intracavernosal injec-▓ha-adrenergic stimulants such as epinephrine and metaraminol has been re-For one case of priapism (of some 12-24 hours' duration) in a DESYREL-treated ▓hom the intracavernosal injection of epinephrine was accomplished, prompt detu-▓occurred with return of normal erectile activity.

▓ure should be performed under the supervision of a urologist or a physician familiar ▓ocedure and should not be initiated without urologic consultation if the priapism has ▓or more than 24 hours.

▓(trazodone hydrochloride) is not recommended for use during the initial recovery ▓myocardial infarction.

▓ould be used when administering DESYREL to patients with cardiac disease, and ▓nts should be closely monitored, since antidepressant drugs (including DESYREL) ▓associated with the occurrence of cardiac arrhythmias. Recent clinical studies in ▓ith pre-existing cardiac disease indicate that DESYREL may be arrhythmogenic in ▓ants in that population. Arrhythmias identified include isolated PVCs, ventricular ▓and in two patients short episodes (3-4 beats) of ventricular tachycardia.

▓ONS

▓ility of suicide in seriously depressed patients is inherent in the illness and may ▓il significant remission occurs. Therefore, prescriptions should be written for the ▓umber of tablets consistent with good patient management.

▓n, including orthostatic hypotension and syncope, has been reported to occur in ▓ceiving DESYREL. Concomitant administration of antihypertensive therapy with ▓may require a reduction in the dose of the antihypertensive drug.

▓own about the interaction between DESYREL and general anesthetics; therefore, ▓ective surgery, DESYREL should be discontinued for as long as clinically feasible.

▓antidepressants, the use of DESYREL should be based on the consideration of the ▓hat the expected benefits of therapy outweigh potential risk factors.

▓n for Patients:

▓riapism has been reported to occur in patients receiving DESYREL, patients with ▓or inappropriate penile erection should immediately discontinue the drug and consult ▓hysician (see WARNINGS).

▓sants may impair the mental and/or physical ability required for the performance of ▓hazardous tasks, such as operating an automobile or machinery; the patient should ▓ed accordingly.

▓may enhance the response to alcohol, barbiturates, and other CNS depressants. ▓should be given shortly after a meal or light snack. Within any individual patient, total ▓ption may be up to 20% higher when the drug is taken with food rather than on an ▓mach. The risk of dizziness/lightheadedness may increase under fasting conditions.

Laboratory Tests:

Occasional low white blood cell and neutrophil counts have been noted in patients receiving DESYREL® (trazodone hydrochloride). These were not considered clinically significant and did not necessitate discontinuation of the drug; however, the drug should be discontinued in any patient whose white blood cell count or absolute neutrophil count falls below normal levels. White blood cell and differential counts are recommended for patients who develop fever and sore throat (or other signs of infection) during therapy.

Drug Interactions:

Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving DESYREL concurrently with either of those two drugs.

It is not known whether interactions will occur between monoamine oxidase (MAO) inhibitors and DESYREL. Due to the absence of clinical experience, if MAO inhibitors are discontinued shortly before or are to be given concomitantly with DESYREL, therapy should be initiated cautiously with gradual increase in dosage until optimum response is achieved.

Therapeutic Interactions:

Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

There have been reports of increased and decreased prothrombin time occurring in Couma-dinized patients who take DESYREL.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving DESYREL in daily oral doses up to 300 mg/kg for 18 months.

Pregnancy Category C:

DESYREL has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat when given at dose levels approximately 30-50 times the proposed maximum human dose. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15-50 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. DESYREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

DESYREL and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when DESYREL is administered to a nursing woman.

Pediatric Use:

Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Because the frequency of adverse drug effects is affected by diverse factors (e.g., drug dose, method of detection, physician judgment, disease under treatment, etc.) a single meaningful estimate of adverse event incidence is difficult to obtain. This problem is illustrated by the variation in adverse event incidence observed and reported from the inpatients and outpatients treated with DESYREL. It is impossible to determine precisely what accounts for the differences observed.

Clinical Trial Reports:

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of DESYREL.

The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those which prevailed in the clinical trials. These incidence figures, also, cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials is conducted under a different set of conditions.

Treatment-Emergent Symptom Incidence

	Inpts.		Outpts.	
	D	P	D	P
Number of Patients	142	95	157	158
% of Patients Reporting				
Allergic				
Skin Condition/Edema	2.8	1.1	7.0	1.3
Autonomic				
Blurred Vision	6.3	4.2	14.7	3.8
Constipation	7.0	4.2	7.6	5.7
Dry Mouth	14.8	8.4	33.8	20.3
Cardiovascular				
Hypertension	2.1	1.1	1.3	*
Hypotension	7.0	1.1	3.8	0.0
Shortness of Breath	*	1.1	1.3	0.0
Syncope	2.8	2.1	4.5	1.3
Tachycardia/Palpitations	0.0	0.0	7.0	7.0
CNS				
Anger/Hostility	3.5	6.3	1.3	2.5
Confusion	4.9	0.0	5.7	7.6
Decreased Concentration	2.8	2.1	1.3	0.0
Disorientation	2.1	0.0	*	0.0
Dizziness/Lightheadedness	19.7	5.3	28.0	15.2
Drowsiness	23.9	6.3	40.8	19.6
Excitement	1.4	1.1	5.1	5.7
Fatigue	11.3	4.2	5.7	2.5
Headache	9.9	5.3	19.8	15.8
Insomnia	9.9	10.5	6.4	12.0
Impaired Memory	1.4	0.0	*	*
Nervousness	14.8	10.5	6.4	8.2
Gastrointestinal				
Abdominal/Gastric Disorder	3.5	4.2	5.7	4.4
Bad Taste in Mouth	1.4	0.0	0.0	0.0
Diarrhea	0.0	1.1	4.5	1.9
Nausea/Vomiting	9.9	1.1	12.7	9.5
Musculoskeletal				
Musculoskeletal Aches/Pains	5.6	3.2	5.1	2.5
Neurological				
Incoordination	4.9	0.0	1.9	0.0
Paresthesia	1.4	0.0	0.0	*
Tremors	2.8	1.1	5.1	3.8
Sexual Function				
Decreased Libido	*	1.1	1.3	*
Other				
Decreased Appetite	3.5	5.3	0.0	*
Eyes Red/Tired/Itching	2.8	0.0	0.0	0.0
Head Full-Heavy	2.8	0.0	0.0	0.0
Malaise	2.8	0.0	0.0	0.0
Nasal/Sinus Congestion	2.8	0.0	5.7	3.2
Nightmares/Vivid Dreams	*	1.1	5.1	5.7
Sweating/Clamminess	1.4	1.1	*	*
Tinnitus	1.4	0.0	0.0	*
Weight Gain	1.4	0.0	4.5	1.9
Weight Loss	*	3.2	5.7	2.5

* Incidence less than 1%.

D = DESYREL   P = Placebo

Occasional sinus bradycardia has occurred in long-term studies.

In addition to the relatively common (i.e., greater than 1%) untoward events enumerated

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above, the following adverse events have been reported to occur in association with the us DESYREL® (trazodone hydrochloride) in the controlled clinical studies: akathisia, allergic n tion, anemia, chest pain, delayed urine flow, early menses, flatulence, hallucinations/delusic hematuria, hypersalivation, hypomania, impaired speech, impotence, increased appetite, creased libido, increased urinary frequency, missed periods, muscle twitches, numbness, retrograde ejaculation.

Postintroduction Reports:

Although the following adverse reactions have been reported in DESYREL users, the cau association has neither been confirmed nor refuted.

Voluntary reports received since market introduction include the following: agitation, alope apnea, ataxia, breast enlargement or engorgement, diplopia, edema, extrapyramidal syi toms, grand mal seizures, hallucinations, hemolytic anemia, hyperbilirubinemia, leukonyc jaundice, lactation, liver enzyme alterations, methemoglobinemia, nausea/vomiting (most quently), paresthesia, priapism (See WARNINGS and PRECAUTIONS, Information for Patie some patients have required surgical intervention), pruritis, psychosis, rash, stupor, inapp priate ADH syndrome, tardive dyskinesia, unexplained death, urinary incontinence, urin retention, urticaria, vasodilation, vertigo and weakness.

Cardiovascular system effects which have been reported include the following: conduct block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, m cardial infarction, cardiac arrest, arrhythmia, and ventricular ectopic activity, including vent ular tachycardia (see WARNINGS).

OVERDOSE

Animal Oral LD$_{50}$

The oral LD$_{50}$ of the drug is 610 mg/kg in mice, 486 mg/kg in rats, and 560 mg/kg in rabb

Signs and Symptoms:

Death from overdose has occurred in patients ingesting DESYREL (trazodone hydrochlori and other drugs concurrently (namely, alcohol; alcohol + chloral hydrate + diazepam; ar barbital; chlordiazepoxide; or meprobamate).

The most severe reactions reported to have occurred with overdose of DESYREL alone h been priapism, respiratory arrest, seizures, and EKG changes. The reactions reported m frequently have been drowsiness and vomiting. Overdosage may cause an increase in incider or severity of any of the reported adverse reactions (see ADVERSE REACTIONS).

Treatment:

There is no specific antidote for DESYREL. Treatment should be symptomatic and supportive the case of hypotension or excessive sedation. Any patient suspected of having taken overdose should have the stomach emptied by gastric lavage. Forced diuresis may be usefu facilitating elimination of the drug.

DOSAGE AND ADMINISTRATION

The dosage should be initiated at a low level and increased gradually, noting the clini response and any evidence of intolerance. Occurrence of drowsiness may require the admir tration of a major portion of the daily dose at bedtime or a reduction of dosage. DESYR should be taken shortly after a meal or light snack. Symptomatic relief may be seen during t first week, with optimal antidepressant effects typically evident within two weeks. Twenty-f percent of those who respond to DESYREL require more than two weeks (up to four weeks) drug administration.

Usual Adult Dosage:

An initial dose of 150 mg/day in divided doses is suggested. The dose may be increased by mg/day every three to four days. The maximum dose for outpatients usually should not exce 400 mg/day in divided doses. Inpatients (i.e., more severely depressed patients) may be giv up to but not in excess of 600 mg/day in divided doses.

Maintenance:

Dosage during prolonged maintenance therapy should be kept at the lowest effective lev Once an adequate response has been achieved, dosage may be gradually reduced, w subsequent adjustment depending on therapeutic response.

Although there has been no systematic evaluation of the efficacy of DESYREL beyond weeks, it is generally recommended that a course of antidepressant drug treatment should continued for several months.

HOW SUPPLIED

DESYREL (trazodone hydrochloride)

Tablets, 50 mg — round, orange/scored, film-sealed (imprinted with DESYREL and MJ 77
   NDC 0087-0775-41 Bottles of 100
   NDC 0087-0775-43 Bottles of 1000
   NDC 0087-0775-42 Cartons of 100 Unit Doses

Tablets, 100 mg — round, white/scored, film-sealed (imprinted with DESYREL and MJ 77
   NDC 0087-0776-41 Bottles of 100
   NDC 0087-0776-43 Bottles of 1000
   NDC 0087-0776-42 Cartons of 100 Unit Doses

Tablets, 150 mg — orange, in the Dividose® tablet design (imprinted with MJ and 778 on fro "50," "50," "50" on reverse)
   NDC 0087-0778-43 Bottles of 100
   NDC 0087-0778-44 Bottles of 500

Tablets, 300 mg — yellow, in the Dividose® tablet design (imprinted with MJ and 796 on fro "100," "100," "100" on reverse)
   NDC 0087-0796-41 Bottles of 100

U.S. Patent No. 4,215,104

Store at room temperature. Protect from temperatures above 104°F (40°C).

Dispense in tight, light-resistant container (USP).

REFERENCES

a. Williams JBW, Ed: Diagnostic and Statistical Manual of Mental Disorders-III, Americ Psychiatric Association May, 1980.
b. Brindley GS: New treatment for priapism, Lancet. July 28, 1984, ii:220.
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THE AMERICAN JOURNAL OF PSYCHIATRY

In this issue:

Turning Points in Twentieth-Century American Psychiatry
By Melvin Sabshin

Evidence of the Role of Psychosocial Factors in Diabetes Mellitus:
A Review
By Jean W. Helz and Bryce Templeton

Her anxiolytic is working— but she's alert, functioning, and at no risk of a benzodiazepine withdrawal syndrome when therapy ends.

That's
Efficacy!

BuSpar® (buspirone HCl)

References: 1. Rickels K, et al. Buspirone and diazepam in anxiety: A controlled study. *J Clin Psychiatry* 1982;43(12, Sec 2):81-86. **2.** Newton RE, et al: A review of the side effect profile of buspirone. *Am J Med* 1986;80(suppl 3B):17-21. **3.** Lucki I, et al: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. **4.** Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(suppl 5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.
Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.
Precautions: *General*—Interference with cognitive and motor performance: Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.
Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.
Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the

syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).
***Information for Patients*—**Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.
***Drug Interactions*—**Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.
***Carcinogenesis, Mutagenesis, Impairment of Fertility*—**No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.
***Pregnancy: Teratogenic Effects*—**Pregnancy Category B: Should be used during pregnancy only if clearly needed.
***Nursing Mothers*—**Administration to nursing women should be avoided if clinically possible.
***Pediatric Use*—**The safety and effectiveness have not been determined in individuals below 18 years of age.
***Use in the Elderly*—**No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.
***Use in Patients with Impaired Hepatic or Renal Function*—**Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.
Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.
***Associated with Discontinuation of Treatment*—**The more common events causing discontinuation in-

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"IT FEELS GOOD TO FEEL USEFUL AGAIN"

For the chronic schizophrenic patient, Navane can mean more competent work performance,[1,2] and a smoother path towards social recovery. Navane may help improve the ability to concentrate, and promote a better attitude toward work and co-workers.[1-3]

Anticholinergic[4] and cardiovascular[5,6] side effects in patients treated with Navane are reported infrequently. Should extrapyramidal symptoms occur, they usually can be controlled.

27% rise in work output compared to baseline shown in patients switched to Navane[2,3]

(Adapted from DiMascio and Demirgian[2,3])

Forty-two psychotic male and female patients under age 55 were entered in this study on a nonblind basis, and randomly assigned to their regular medication or switched to thiothixene. Patients were evaluated at baseline and on a daily basis, and periodically rated on the Global Improvement and Brief Psychiatric Rating Scales.

In schizophrenia,

Navane® (thiothixene) (thiothixene HCl)

Please see brief summary of NAVANE® (thiothixene/thiothixene HCl) prescribing information on adjacent page.

Navane®

(thiothixene) (thiothixene HCl)

It feels good to feel useful again

Capsules — 1 mg, 2 mg, 5 mg, 10 mg, 20 mg

Intramuscular 2 mg/ml 5 mg/ml

Concentrate 5 mg/ml

References: 1. Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2. DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3. DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association. Washington, DC, May 3-6, 1971. 4. Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry.* Basel, Switzerland, S. Karger, 1969, vol 2, pp 45-52. 5. Dillenkoffer RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of the American Psychiatric Association, Dallas, May 1-4, 1972. 6. Data available on request from Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml
Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.
Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.
Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.
Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.
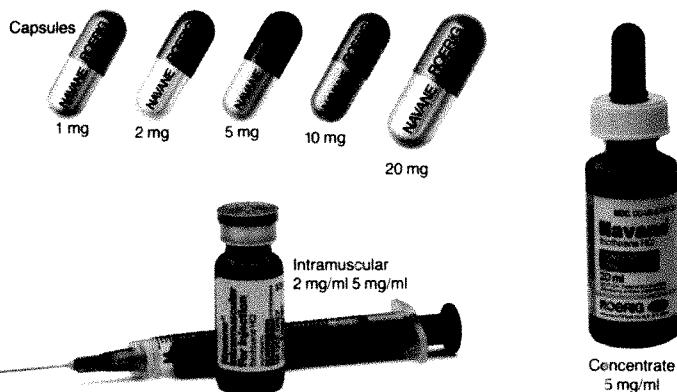
Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.
Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.
Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.
Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

ROERIG *Pfizer*

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Coming in the November 1990 issue of

THE AMERICAN JOURNAL OF PSYCHIATRY

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*A Critical Review of Epidemiological Studies
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Unique... Specific...

Prozac® (fluoxetine hydrochloride)
is the first highly specific,
highly potent blocker
of serotonin uptake

PR⊙ZAC®
fluoxetine hydrochloride

The antidepressant most frequently prescribed by psychiatrists in the United States[1]

See adjacent page for brief summary of prescribing information.

1. Based on independent market research data, December 1988-February 1990.

Prozac® (fluoxetine hydrochloride)

Brief Summary.
Consult the package insert for complete information.

Indications: For the treatment of depression.

Contraindication: Known hypersensitivity to Prozac.

Warnings: *Monoamine Oxidase Inhibitors* — The combined use of fluoxetine and MAO inhibitors should be avoided. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of an MAOI. Serious events, including death, have been reported to occur following the initiation of an MAOI shortly after discontinuation of fluoxetine.

Rash and Possibly Allergic Events — Approximately 4% of 5,600 fluoxetine patients developed a rash and/or urticaria in premarketing testing. Almost a third of these discontinued therapy because of rash and/or associated systemic signs or symptoms. Reported in association with rash were fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly upon discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all were reported to recover completely.

Of two patients who developed a serious cutaneous systemic illness during premarketing clinical trials, one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome considered variously as a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events possibly related to vasculitis have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or represent immunologic responses is not known. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

Precautions: *General* — Anxiety, Nervousness, and Insomnia — Reported by 10% to 15% of patients, 5% of whom discontinued fluoxetine.

Altered Appetite and Weight — Significant weight loss, especially in underweight patients, may be an undesirable result of treatment.

Approximately 9% of fluoxetine patients experienced anorexia in controlled clinical trials, an incidence approximately sixfold that seen with placebo. A weight loss >5% of body weight occurred in 13% of fluoxetine patients compared with 4% in those on placebo and 3% in those on tricyclics. However, only rarely did fluoxetine patients discontinue treatment because of weight loss.

Activation of Mania/Hypomania — Hypomania or mania occurred in approximately 1% of fluoxetine patients in premarketing testing.

Seizures — Twelve of 6,000 patients (0.2%) experienced convulsions (or, possibly, seizures). Prozac should be introduced with care in patients with a history of seizures.

Suicide — Close supervision of high-risk patients should accompany initial therapy. Prescriptions of Prozac should be written for the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites — Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment.

Use in Patients with Concomitant Illness — Caution is advisable in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. ECGs of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis, the clearances of fluoxetine and its active metabolite were decreased. A lower or less frequent dose should be used in patients with cirrhosis.

Fluoxetine should be used with caution in patients with severe renal impairment. In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation. Insulin and/or oral hypoglycemic dosage may need to be adjusted when fluoxetine therapy is instituted or discontinued.

Interference with Cognitive and Motor Performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug does not affect them adversely.

Information for Patients — Physicians should advise their patients to notify them if they:
- are taking or plan to take any prescription or over-the-counter drugs or alcohol
- become pregnant or intend to become pregnant during therapy
- are breast feeding an infant
- develop a rash or hives

Drug Interactions — Tryptophan — Five patients receiving tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors — See Warnings.

Other Antidepressants — There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents.

Lithium — There have been reports of both increased and decreased lithium levels and lithium toxicity. Lithium levels should be monitored.

Diazepam Clearance — The half-life of diazepam may be prolonged in some patients.

Drugs Tightly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma protein, the concurrent administration of fluoxetine and another tightly bound drug may cause a shift in plasma concentrations potentially resulting in an adverse effect. Adverse effects may also result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs — Caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy — There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility — There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at doses approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively revealed no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies in rats at doses approximately five and nine times the maximum human dose (80 mg) respectively revealed no adverse effects on fertility. A slight decrease in neonatal survival was noted, probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy — Teratogenic Effects — Pregnancy Category B — Reproduction studies in rats and rabbits at doses nine and 11 times the maximum human dose (80 mg) respectively revealed no evidence of harm to the fetus. Although there have been no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery — The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers — Because Prozac is known to be excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children — Safety and effectiveness in children have not been established.

Usage in the Elderly — In clinical studies of several hundred elderly patients, no unusual adverse age-related phenomena were identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients with concomitant systemic illnesses or those receiving concomitant drugs.

Hyponatremia — Hyponatremia (some cases with serum Na <110 mmol/L) has been reported, which appeared to be reversible on drug discontinuation. Some cases were possibly due to SIADH, and the majority have been in older patients and those taking diuretics or otherwise volume depleted.

Platelet Function — There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

Adverse Reactions: *Commonly Observed* — Nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment — Fifteen percent of 4,000 clinical trial patients discontinued fluoxetine due to an adverse event. The more common events included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials — The accompanying table enumerates adverse events that occurred at a frequency of ≥ 1% in controlled trials.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Prozac (N = 1,730)	Placebo (N = 799)	Body System/ Adverse Event*	Prozac (N=1,730)	Placebo (N=799)
Nervous			**Body as a Whole**		
Headache	20.3	15.5	Asthenia	4.4	4.5
Nervousness	14.9	8.5	Infection, viral	3.4	3.1
Insomnia	13.8	7.1	Pain, limb	1.6	1.1
Drowsiness	11.6	6.3	Fever	1.4	—
Anxiety	9.4	5.5	Pain, chest	1.3	1.1
Tremor	7.9	2.4	Allergy	1.2	1.1
Dizziness	5.7	3.3	Influenza	1.2	1.5
Fatigue	4.2	1.1	**Respiratory**		
Sedated Sensation	1.9	1.3	Upper respiratory		
disturbance	1.7	2.0	infection	7.6	6.0
Libido,			Flu-like		
decreased	1.6	—	syndrome	2.8	1.9
Light-			Pharyngitis	2.7	1.3
headedness	1.6	—	Nasal		
Concentration,			congestion	2.6	2.3
decreased	1.5	—	Headache,		
Digestive			sinus	2.3	1.8
Nausea	21.1	10.1	Sinusitis	2.1	2.0
Diarrhea	12.3	7.0	Cough	1.6	1.6
Mouth			Dyspnea	1.4	—
dryness	9.5	6.0	**Cardiovascular**		
Anorexia	8.7	1.5	Hot flushes	1.8	1.0
Dyspepsia	6.4	4.3	Palpitations	1.3	1.4
Constipation	4.5	3.3	**Musculoskeletal**		
Pain,			Pain, back	2.0	2.4
abdominal	3.4	2.9	Pain, joint	1.2	1.1
Vomiting	2.4	1.3	Pain, muscle	1.2	1.0
Taste change	1.8	—	**Urogenital**		
Flatulence	1.6	1.1	Menstruation,		
Gastroenteritis	1.0	1.4	painful	1.9	1.4
Skin and			Sexual		
Appendages			dysfunction	1.9	—
Sweating,			Frequent		
excessive	8.4	3.8	micturition	1.6	—
Rash	2.7	1.8	Urinary tract		
Pruritus	2.4	1.4	infection	1.2	—
			Special Senses		
			Vision		
			disturbance	2.8	1.8

*Events reported by ≥1% of fluoxetine patients are included.
— Incidence <1%

Other Events Observed During Premarketing Evaluation in 5,600 Fluoxetine Patients — Frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole — Frequent: chills; Infrequent: chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; Rare: abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System — Infrequent: angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; Rare: AV block first-degree, bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System — Frequent: increased appetite; Infrequent: aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, thirst; Rare: bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System — Infrequent: hypothyroidism; Rare: goiter and hyperthyroidism.

Hemic and Lymphatic System — Infrequent: anemia and lymphadenopathy; Rare: bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional — Frequent: weight loss; Infrequent: generalized edema, hypoglycemia, peripheral edema, and weight gain; Rare: dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System — Infrequent: arthritis, bone pain, bursitis, tenosynovitis, and twitching; Rare: bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System — Frequent: abnormal dreams and agitation; Infrequent: abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; Rare: abnormal electro-encephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System — Frequent: bronchitis, rhinitis, and yawn; Infrequent: asthma, epistaxis, hiccup, hyperventilation, and pneumonia; Rare: apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages — Infrequent: acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; Rare: eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses — Infrequent: amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; Rare: blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System — Infrequent: abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; Rare: abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports — Voluntary reports of adverse events temporarily associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: cerebral vascular accident, confusion, dyskinesia, ecchymoses, gastrointestinal hemorrhage, hyperprolactinemia, pancreatitis, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, and violent behaviors.

Overdosage: *Human Experience* — As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. A second death involved fluoxetine, codeine, and temazepam.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment. The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

A single death attributed to overdose of fluoxetine alone has been reported.

PV 2478 DPP   [052490]

Additional information available to the profession upon request.

Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46285

FL-4921-T-049327

Prozac® (fluoxetine hydrochloride, Dista)

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Prozac® (fluoxetine hydrochloride, Dista)

Reduce the risk of life-style disruptions that can interfere with therapy for depression.

Start with Wellbutrin to help clear depression with few life-style disruptions.

Relieves depression effectively.

Therapeutically equivalent to amitriptyline with no differences in the frequency, degree, or rate of response.[1]

Little or no daytime drowsiness.

Patients treated with WELLBUTRIN experienced sedation less often than those treated with amitriptyline or doxepin.[2,3]

Few anticholinergic side effects.

Patients experienced troubling side effects, such as dry mouth and constipation, less often than those treated with either doxepin or amitriptyline.[2,3]

No clinically significant effect on cardiac conduction.

No significant changes in any measured ECG parameter. A substantially wider margin of safety than amitriptyline with respect to cardiac conduction.[4]

No clinically significant orthostatic hypotension.

No clinically significant orthostatic hypotension in patients with preexisting cardiac disease or in healthy depressed patients who had experienced orthostatic hypotension when treated with tricyclics.[5,6]

Important Considerations

The most common side effects of WELLBUTRIN are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor. The principal medically important adverse reaction with WELLBUTRIN is seizure, for which the incidence is approximately four-tenths of one percent (4/1,000). This incidence may exceed that of other marketed antidepressants. For more information, see brief summary of full prescribing information on last page of this advertisement, especially the WARNINGS section regarding the incidence of seizures and the recommendations for reducing the risk.

References: 1. Mendels J, Amin MM, Chouinard G, et al. A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry.* 1983;44(5, sec 2):118-120. **2.** Feighner J, Hendrickson G, Miller L, Stern W. Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. *J Clin Psychopharmacol.* 1986;6:27-32. **3.** Data on file, Burroughs Wellcome Co., 1989. **4.** Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry.* 1983;44(5, sec 2):174-175. **5.** Farid FF, Wenger TL, Tsai SY, Singh BN, Stern WC. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. *J Clin Psychiatry.* 1983;44(5, sec 2):170-173. **6.** Roose SP, Glassman AH, Giardina EGV, Johnson LL, Walsh BT, Bigger JT Jr. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. *J Clin Psychopharmacol.* 1987;7:247-251.

Feeling better
living better

Wellbutrin®
(BUPROPION HCl)

See brief summary of full prescribing information on last page of this advertisement.

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Wellbutrin is indicated for the treatment of depression. A physician considering the initiation of Wellbutrin should be aware that the drug may cause generalized seizures with an approximate incidence of 0.4% (4/1000). This incidence may exceed that of other antidepressants as much as fourfold. This relative risk is only an approximation since no direct comparative studies have been conducted.

CONTRAINDICATIONS: Wellbutrin is contraindicated in patients: with a seizure disorder; with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in such patients; who have shown an allergic response to it; or who are currently being treated with an MAO inhibitor. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

WARNINGS: SEIZURES: Wellbutrin is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the pre-approval evaluation period, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight (8) seizures occurred during the initial 8 week treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

Recommendations for reducing the risk of seizure: Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if (1) the total daily dose of Wellbutrin does *not* exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose *not* to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when Wellbutrin is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

PRECAUTIONS: General:

Agitation and Insomnia: A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

Use in Patients with Systemic Illness: There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups.

Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients: Consult complete product information.

Drug Interactions: No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.

However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality.) There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of Wellbutrin on labor and delivery in humans is unknown.

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of Wellbutrin in individuals under 18 years old have not been established.

Use in the Elderly: Wellbutrin has not been systematically evaluated in older patients.

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in the product's pre-approval clinical trials. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600 mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in the WARNINGS and PRECAUTIONS sections.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS* (Percent of Patients Reporting)

Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)	Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)
CARDIOVASCULAR			Dry Mouth	27.6	18.4
Cardiac Arrhythmias	5.3	4.3	Excessive Sweating	22.3	14.6
Dizziness	22.3	16.2	Headache/Migraine	25.7	22.2
Hypertension	4.3	1.6	Impaired Sleep Quality	4.0	1.6
Hypotension	2.5	2.2	Increased Salivary Flow	3.4	3.8
Palpitations	3.7	2.2	Insomnia	18.6	15.7
Syncope	1.2	0.5	Muscle Spasms	1.9	3.2
Tachycardia	10.8	8.6	Pseudoparkinsonism	1.5	1.6
DERMATOLOGIC			Sedation	19.8	19.5
Pruritus	2.2	0.0	Sensory Disturbance	4.0	3.2
Rash	8.0	6.5	Tremor	21.1	7.6
GASTROINTESTINAL			**NEUROPSYCHIATRIC**		
Anorexia	18.3	18.4	Agitation	31.9	22.2
Appetite Increase	3.7	2.2	Anxiety	3.1	1.1
Constipation	26.0	17.3	Confusion	8.4	4.9
Diarrhea	6.8	8.6	Decreased Libido	3.1	1.6
Dyspepsia	3.1	2.2	Delusions	1.2	1.1
Nausea/Vomiting	22.9	18.9	Disturbed Concentration	3.1	3.8
Weight Gain	13.6	22.7	Euphoria	1.2	0.5
Weight Loss	23.2	23.2	Hostility	5.6	3.8
GENITOURINARY			**NONSPECIFIC**		
Impotence	3.4	3.1	Fatigue	5.0	8.6
Menstrual Complaints	4.7	1.1	Fever/Chills	1.2	0.5
Urinary Frequency	2.5	2.2	**RESPIRATORY**		
Urinary Retention	1.9	2.2	Upper Respiratory Complaints	5.0	11.4
MUSCULOSKELETAL					
Arthritis	3.1	2.7	**SPECIAL SENSES**		
NEUROLOGICAL			Auditory Disturbance	5.3	3.2
Akathisia	1.5	1.1	Blurred Vision	14.6	10.3
Akinesia/Bradykinesia	8.0	8.6	Gustatory Disturbance	3.1	1.1
Cutaneous Temperature Disturbance	1.9	1.6			

*Events reported by at least 1% of Wellbutrin patients are included.

Other events observed during the entire pre-approval evaluation of Wellbutrin: During its pre-approval assessment, Wellbutrin was evaluated in almost 2400 subjects. The conditions and duration of exposure to Wellbutrin varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; and rare were pallor and phlebitis.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color and hirsutism.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, G.I. bleeding, and intestinal perforation.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare was lymphadenopathy.

Neurological: (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; and rare were EEG abnormality, abnormal neurological exam, impaired attention, and sciatica.

Neuropsychiatric: (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis and rate or rhythm disorder.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction and overdose.

Post-Approval Reports: The following additional events were rarely observed (less than 1/1000 patients) post-approval:

Cardiovascular: Flushing and myocardial infarction.

Dermatologic: Acne.

Gastrointestinal: Stomach ulcer.

Hematologic/Oncologic: Anemia and pancytopenia.

Neurological: Aphasia.

Musculoskeletal: Musculoskeletal chest pain.

Respiratory: Pneumonia and pulmonary embolism.

DOSAGE AND ADMINISTRATION: General Dosing Considerations: It is particularly important to administer Wellbutrin in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3 day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

No single dose of Wellbutrin should exceed 150 mg. Wellbutrin should be administered t.i.d., preferably with at least 6 hours between successive doses.

Usual Dosage for Adults: The usual adult dose is 300 mg/day, given t.i.d. Dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg t.i.d., sooner than 3 days after beginning therapy (see table below).

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of Wellbutrin may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.d. with at least 4 hours between successive doses in order not to exceed the limit of 150 mg in a single dose. Wellbutrin should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

Elderly Patients: In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs.

Burroughs Wellcome Co.
Wellcome Research Triangle Park, NC 27709

CLOZARIL® (clozapine): Fulfilling the Promise With CPMS℠

This is a case report about "Michael" — 1 of 20 patients whose lives may have been saved by the Clozaril Patient Management System℠ (CPMS) in the first six months of commercial availability of CLOZARIL® (clozapine).

Michael is 35 years old. A few years ago he was diagnosed as having chronic undifferentiated schizophrenia. He was demonstrating poor judgment, paranoid delusions, auditory hallucinations, disorganization of thought, and inappropriate laughter. His symptoms were not controlled by standard antipsychotic agents, so in early May Michael began treatment with CLOZARIL, the breakthrough antipsychotic agent. Because 1% to 2% of CLOZARIL patients develop agranulocytosis, a potentially fatal blood disorder, the drug is available only through CPMS — a program that links drug distribution to mandatory weekly blood tests (no blood, no drug).

Throughout the month of May, weekly blood tests performed by the specially trained CPMS team showed that Michael's white blood cell (WBC) counts were within the normal range but fluctuating downward. Michael's CPMS case administrator continued to coordinate his monitoring: obtaining weekly blood samples and reporting tests results. On June 12, monitoring showed he had developed mild leukopenia (3600/mm³). His case administrator immediately reported the results to Michael's physician, who decided to interrupt CLOZARIL therapy. In most leukopenic patients this step results in gradual normalization of the WBC count; however, in Michael's case, subsequent CPMS tests revealed otherwise.

Whenever CLOZARIL therapy is discontinued, CPMS staff members continue hematologic monitoring of the patient for four consecutive weeks. On June 26, two weeks after CLOZARIL therapy was stopped, this added safety measure detected that Michael's WBC count had fallen to 1400/mm³ and his granulocyte count to 238/mm³. Even though he had discontinued treatment, he developed agranulocytosis. The results were reported immediately to his phy-

sician and other members of the healthcare team, who placed Michael in protective isolation and instituted medical treatment. Serving as both a coordinator and liaison, the CPMS case administrator worked closely with the hospital team to arrange daily blood testing for Michael — often working around the clock to obtain and report lab results.

By July 5 the agranulocytosis had reversed completely, and Michael was discharged from the medical unit and admitted to a psychiatric ward. Today Michael is receiving another antipsychotic agent. He remains symptomatic, but thanks to the special safety precautions initiated by CPMS, his life was saved.

As exemplified in this case study, CPMS is an early warning system designed and implemented to help prevent fatalities by detecting agranulocytosis in a timely manner. By using a fully dedicated national staff with rigid quality control standards, CPMS links CLOZARIL distribution to mandatory weekly blood tests. Furthermore, because agranulocytosis is likely to recur rapidly in patients such as Michael, who have proven sensitive to CLOZARIL (clozapine), CPMS maintains a national database that tracks all patients and thus limits the possibility of reexposure — even if they relocate from one state to another.

Compliance is another key to the successes of CPMS. The CPMS patient-monitoring compliance rate has been over 97% since February 1990. During that time 20 cases of agranulocytosis have occurred. With the mandatory blood monitoring of CPMS all cases were detected; and with timely discontinuation of the drug all patients have recovered uneventfully.

CLOZARIL (clozapine) provides new hope for severely ill schizophrenic patients. CPMS helps to assure safe fulfillment of this hope; experience has shown that it provides the high level of safety to which patients are entitled. Although the therapeutic hope of CLOZARIL (clozapine) was unfulfilled for Michael, happily, the promise of CPMS was.

Sandoz Pharmaceuticals Corporation
E. Hanover, NJ 07936

CLOZARIL®

(clozapine)

TABLETS

CAUTION: Federal law prohibits dispensing without a prescription.

CONTRAINDICATIONS

CLOZARIL is contraindicated in patients with myeloproliferative disorders, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. CLOZARIL should not be used simultaneously with other agents having a well-known potential to suppress bone marrow function. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

WARNINGS

General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZARIL MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR FOUR WEEKS AFTER THE DISCONTINUATION OF CLOZARIL.

CLOZARIL IS AVAILABLE ONLY THROUGH THE CLOZARIL PATIENT MANAGEMENT SYSTEM℠ (CPMS℠).

Agranulocytosis

Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm³, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1986, 35% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.

Treatment should not be initiated if the WBC count is less than 3500 per mm³, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm³ or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm³, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm³ and a granulocyte count above 1500 per mm³, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000 per mm³ or the granulocyte count below 1500 per mm³, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm³ and the granulocyte count returns to levels above 1500 per mm³. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm³.

If the total WBC count falls below 2000 per mm³ or the granulocyte count falls below 1000 per mm³, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000 per mm³, or granulocyte counts below 1000 per mm³ during CLOZARIL therapy should *not* be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).

Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.

To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.

Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL.

CLOZARIL
(clozapIne)
TABLETS

Drug Interactions

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function. Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs. Because CLOZARIL is highly bound to serum protein, the administration of CLOZARIL to a patient taking another drug which is highly bound to protein (e.g., warfarin, cigoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL by other highly bound drugs.

CLOZARIL may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

ADVERSE REACTIONS

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of 5% or greater were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

DOSAGE AND ADMINISTRATION

Initial Treatment

It is recommended that treatment with CLOZARIL begin at 25 mg once or twice daily, and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of two weeks. Subsequent dosage increments should be made no more than once- or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL in treatment resistant patients, the mean and median CLOZARIL doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

Discontinuation of Treatment

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1. to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

CLOZARIL is available only through the Clozaril Patient Management System, a program that combines white blood cell testing, patient monitoring, pharmacy, and drug distribution services, all linked to compliance with required safety monitoring.

To prescribe CLOZARIL call 1-800-237-CPMS (2767) or mail in a completed CPMS Enrollment Form.

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Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.

DECEMBER

December 7–9, World Congress on AIDS, "HIV: The Future of an Epidemic," Bombay. Contact Chairman, Organizing Committee, World Congress on AIDS, 1/F, Tulsi Bhuvan, Block:1, 23, Bhulabhai Desai Road, Bombay 400 026, India; 91-22-8519020.

December 10–15, annual meeting, American College of Neuropsychopharmacology, Maui, Hawaii. Contact Oakley Ray, Ph.D., Secretary, Box 1823-Station B, Nashville, TN 37221; 615-327-7200.

December 11–14, 8th International Psychiatric Conference, Pakistan Psychiatric Society, Islamabad, Pakistan. Contact: Professor Malik H. Mubbashar, Organizing Committee Chair, 8th International Psychiatric Conference, Department of Psychiatry, Rawalpindi General Hospital, Rawalpindi, Pakistan.

December 12–16, annual meeting, Milton H. Erickson Foundation, Inc., Anaheim, California. Contact Jeffrey K. Zeig, Ph.D., Director, 3606 North 24th Street, Phoenix, AZ 85016; 602-956-6196.

JANUARY

January 20–26, 18th Annual Meeting, Southern Clinical Neurological Society, "Advances in Neurology," Cancun, Mexico. Contact Millie F. Walden, Executive Secretary, 3425 S.W. 2nd Avenue, #154, Gainesville, FL 32607; 904-373-9765.

January 31–February 2, 14th Annual Meeting, Neurology for Non-Neurologists, San Diego. Contact Edith S. Bookstein, Neurology for Non-Neurologists, Inc., P.O. Box 2586, La Jolla, CA 92038; 619-454-3212.

FEBRUARY

February 21–24, American Society on Addiction Medicines' Fifth National Forum on AIDS and Chemical Dependency, San Francisco. Contact: Meeting and Travel Services, Inc. 404-458-3382.

February 22–23, 1st European Symposium on Drug Addiction and AIDS, Vienna. Contact Dr. Norbert Loimer, Waehringer Guertel 18-20, A-1090 Vienna, Austria; 43-1-40400-35 75.

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March 6–9, annual meeting, Association for Academic Psychiatry, Tampa, FL. Contact Ms. O'Loughlin, Department of Psychiatry, Mount Auburn Hospital, Cambridge, MA 02238; 617-499-5198.

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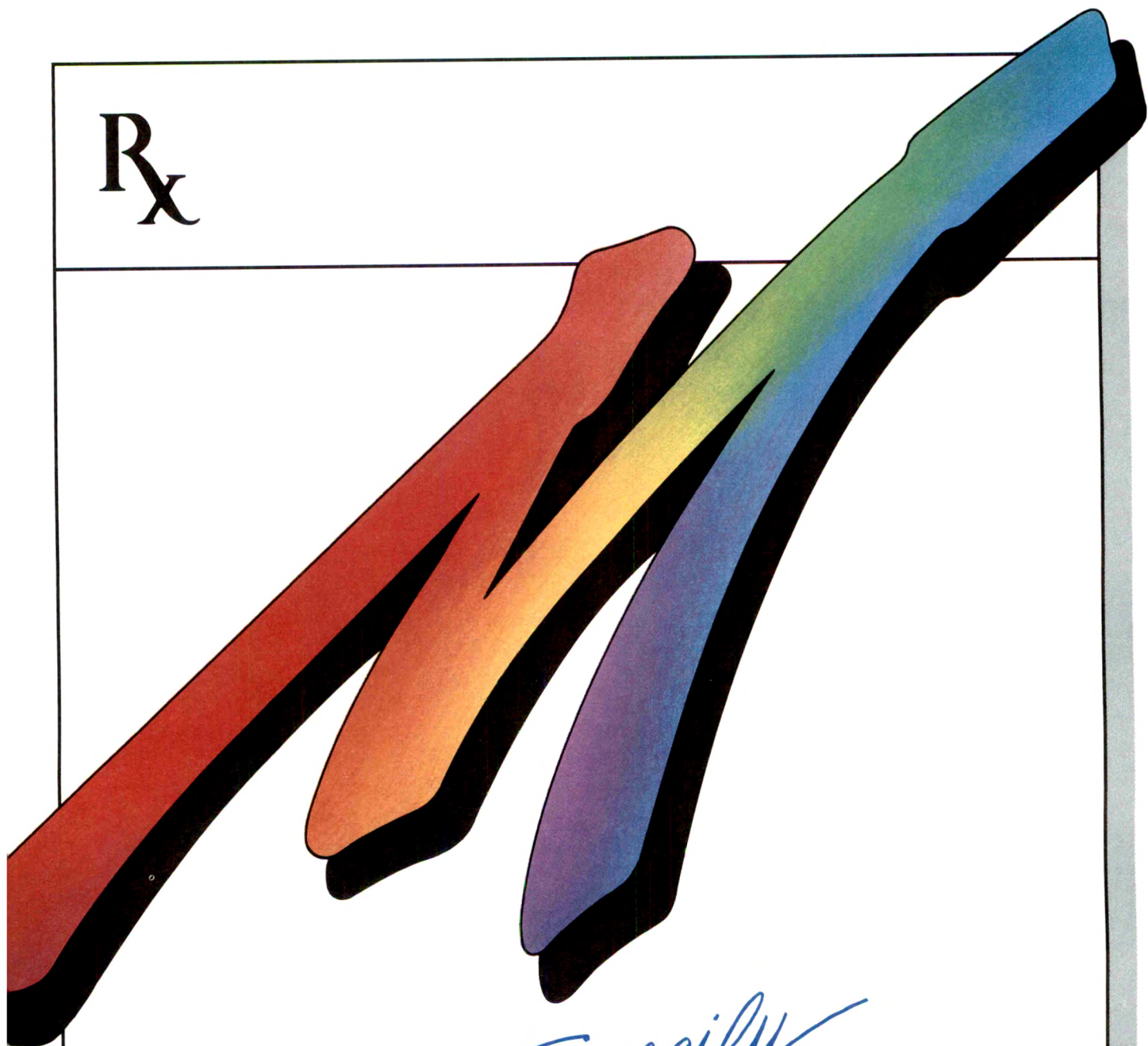
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Turning Points in Twentieth-Century American Psychiatry

Melvin Sabshin, M.D.

The author examines four major turning points in twentieth-century American psychiatry, emphasizing the movement during the post-World War II period toward a psychotherapeutic/psychoanalytic approach and the emergence of biological psychiatry, neuroscience, and logical positivism during the 1970s and 1980s. He discusses the impact of Adolf Meyer during the mid-twentieth century and his ongoing influence. The final turning point involves a prediction of a late twentieth-century change, including new directions in nosology, emphasis on combined pharmacotherapeutic/psychotherapeutic treatments, efforts to create alternatives to full inpatient care, better outcome data for psychiatric treatments, and beginning resolution of major boundary problems of current practice.
(Am J Psychiatry 1990; 147:1267–1274)

In 1966, on the occasion of the centenary of Adolf Meyer's birth, Theodore Lidz delivered the Meyer lecture, entitling it "Adolf Meyer and the Development of American Psychiatry" (1). He concluded the published version of the paper by saying, "In commemorating him, we can do much for ourselves and for psychiatry by recognizing and utilizing the heritage he left us." Analogously, in 1980 John Neill reviewed Meyer's contributions in a paper on "Adolf Meyer and American Psychiatry Today" (2). He stated, "Meyer's

times were similar to ours in many ways. In a curious fashion our professional wheel has come full circle to where it was in 1900, and we are again in need of the Meyerian spirit, a holistic perspective. Acquainting ourselves with the wisdom in his legacy is an important first step on the journey forward." In the 1985 Adolf Meyer lecture, Michael Rutter (3) pointed out the relevance of Meyer's work to major current issues in psychiatry. His paper, entitled "Meyerian Psychobiology, Personality Development, and the Role of Life Experiences," clearly enunciated the fundamental implications of the psychobiological concept. In this paper, I wish to follow my eminent predecessors but also to delineate in my own way how a reexamination of these Meyerian concepts might point the way toward the next turning point in American psychiatry. Indeed, I perceive subtle signs of the early phases around which the next stage might coalesce, and I anticipate that by the beginning of the twenty-first century, the developmental lines will be much clearer.

To be the Medical Director of APA is in itself a remarkable honor, and I have consistently relished the opportunity to be part of the profession's adaptation to new forces from within and outside of its changing boundaries. Lidz stated that "Adolf Meyer virtually identified himself with psychiatry"(1), and I empathize with that position as long as it is understood that I have also maintained the differentiation.

Of late I have noted the tendency (not yet a symptom) to reminisce and reflect about the broader sweep of events; indeed, I have been a participant and observer in remarkable changes in our field. In this paper, I wish to review some of these events with emphasis upon the post-World War II changes that have been part of my personal experience. The scientific program of APA's 1989 annual meeting is an excellent symbol of our current status—quite different from the symbols and substance of the meetings of a quarter of a century ago. In this paper, I wish to highlight four turning

points: 1) the rise of Meyerian psychobiology and its peak impact in the second quarter of the twentieth century, 2) the dominance of divergent therapeutic ideologies, including the important impact of psychoanalysis in the post-World War II years, 3) the current surge of neuroscience and psychopharmacology along with empiricism and logical positivism, 4) a predicted reemergence of analogues of Meyerian psychobiology at the turn of the twenty-first century accompanied by a) a new systematized psychobiology of coping, of adaptation, and of active efforts by persons to deal with multileveled stresses, b) an increased knowledge base in life course transactions converting the elaborate Meyerian history taking system to a more dynamic and relevant process, c) a trend toward a new nosological system that will give life and greater utility to the current axis IV and V systems (*DSM-III* and *DSM-III-R*) and will deal more effectively with the boundaries between health and disorder, d) with a, b, and c (coping, life history, and boundaries between health and illness), and accompanied by appropriate professional leadership, the reemergence of a vital new clinical psychiatry, e) a more balanced overall approach using psychoanalytic, social psychiatric, and biological concepts that have become clear enough to test empirically, and f) a more rational therapeutic system emphasizing new combinations and transactions between pharmacotherapy and psychotherapy—along with a new generation of educators experienced in these combinations.

THE RISE OF MEYERIAN PSYCHOBIOLOGY AND ITS PEAK IMPACT IN THE SECOND QUARTER OF THE TWENTIETH CENTURY

I entered psychiatry in the decade after World War II. The winds of change had already altered the psychiatric landscape, and almost all of my clinical supervisors and teachers espoused the new "dynamic psychiatry." The textbooks of psychiatry, however, were still dominated strongly by the prewar developments, and my introduction to Adolf Meyer was influenced primarily by written words rather than by clinical interactions and case conferences or personal contact. In retrospect, I understand that this was unfortunate because it was not easy to grasp Meyer's ideas from his written words alone. Henderson (4) said that "Adolf Meyer had to surmount language difficulties affecting his speech and his writing which made it far from easy to get his meaning and rendered his ideas more obscure than they really were." Ebaugh (5), commenting on the same subject, stated that "It was frequently difficult to grasp the full import of Dr. Meyer's formulations. It was his tendency to be elliptical or to verbalize incomplete thoughts which meandered in the direction of his own special interest of the moment. This may account, in part, for the fact that his theories are not fully recorded, or are, at best, inadequately understood." (It is hoped that late twentieth-century technology will afford subsequent generations an opportunity to learn

from current theorist leaders by ways other than written words.) Over time, however, I have become increasingly knowledgeable about the basic tenets of Meyer's ideas and understand better what a pervasive influence he exerted. Even more important for me, I began to understand why his ideas were so important. It is hoped that others will find it rewarding to make their own judgments on this matter.

On several occasions, Meyer sketched his own perception of the historical phases of psychiatry in the United States (6). He tended to call the first phase "the time of the Thirteen," honoring the founders of APA. He then described the second phase as "the preoccupation with the brain (a mere word with most) as the palpable issue in the disorder, when the workers actually looked for new emphases and concrete methods having to regulate complex organismal wholes, and the rising of competition from outside after the Civil War." That prototypic Meyerian description, with all of its ambiguity, lies at the heart of his concerns, namely, that the biological reductionism in the late nineteenth century was, at least in part, a defensive maneuver against the influx of immigrants into the United States. The "moral psychiatry" of the earlier part of the nineteenth century was fine with Yankee patients and doctors but somehow less appropriate with postindustrial America. In characterizing a third phase of American psychiatry from the 1890s to World War I, Meyer essentially described a period of increased systematization of research, followed by a fourth phase that was a description of some of his hopes and aspirations. Meyer highlighted the development of special psychiatric centers (research oriented institutes) that could be models for an advancing science of psychiatry. His thoughts about psychosomatic processes and psychiatry's role in medicine were enunciated with emphasis upon "the person" and strong criticism of dualism and reductionism.

From our late twentieth century vantage point, the nuances of changes in the first part of this century are overshadowed by a dominant trend symbolized by Meyer himself. Indeed, the turning point that peaked in the second quarter of this century can be characterized as a gradual shift from the prior biological reductionism and its attendant practices and value systems to a phase where clinical psychiatry took on new aspirations, new methods, and new interests. While Meyer characterized his major approach as psychobiology, his personal style reflected the biopsychosocial model as enunciated much later by Engel (7). When finally ensconced in his pivotal professorship at Johns Hopkins (Phipps Clinic), Meyer maintained a profound interest in clinical practice, carried out experimental procedures in the anatomical laboratories adjacent to his office, became the preeminent educator of the psychiatric leaders of the next generation, and continuously served as an ardent advocate of community programs. Simultaneously, he collaborated with leaders in other clinical departments to develop psychosomatic programs (including liaison activities) and also

kept abreast of larger philosophic, social, and political events. Keeping abreast was not an extraneous abstraction but involved friendship and collaboration with an impressive array of scholars, politicians, and moral philosophers.

It is likely, of course, that American psychiatry would have changed direction even without Meyer, but its contour and evolution were deeply influenced by him. It took a very special leader, however, to effect a turning of psychiatry toward a new direction. His solid biological roots gave special credence to his emphasis upon the patient as a person; simultaneously, his interest in social and community phenomena could not be brushed away as irrelevant abstractions. Kraepelin and his American counterparts had been challenged by a worthy critic who shook the lugubrious roots of the concept of dementia praecox. S. Weir Mitchell's 1894 challenge (8) to psychiatry to solidify its scientific and medical foundations was being answered by a leader with impeccable medical and scientific credentials. A mood of hope and of increasing capacity to cope with the enormous problems began to spread through the new scientific and academic institutes created by Meyer and his students. Many of these students became the directors and chairs of the major psychiatric departments across the country and also overseas. As they began to confront the many issues, however, progress was not easy. Hundreds of thousands of patients were housed in deteriorating institutions; treatment techniques and methods were unspecific; and the number of trained practitioners was much too small for the demands upon them. Just as the first rays of light began to seep through the end of the tunnel, World War II occurred and American psychiatry became absorbed in a momentous maelstrom that challenged many fundamental tenets.

THE DOMINANCE OF DIVERGENT THERAPEUTIC IDEOLOGIES INCLUDING THE IMPORTANT IMPACT OF PSYCHOANALYSIS IN THE POST-WORLD WAR II YEARS

World War II produced massive upheavals beyond the preemptive political and military events that changed the future course of history. In the wake of larger changes, old boundaries and barriers between nations became more permeable so that both people and ideas moved from one part of the world to another. The movement included the emigration of brilliant psychoanalysts to Western Europe, the United States, and Canada.

For American psychiatry these events precipitated significant qualitative changes that have been well documented in many excellent publications. In this paper I wish to emphasize a few aspects of these changes, which, at least in part, have not been emphasized enough.

The large number of American psychiatric casualties among our troops had riveted public attention to what

began to be understood as a serious national problem. Wide publicity about new techniques to deal with traumatic neuroses, as developed by an able cadre of military psychiatrists, also had a significant impact. (I was fortunate enough to work for many years with Roy Grinker [9] and learned much about those heady days.)

What I wish to emphasize in this paper is that all of these postwar changes were engrafted upon the predisposing tendencies engendered during the Meyerian turning point. The uncompleted psychobiological revolution had opened new possibilities to concentrate upon the person and upon the individual clinical case. Biological psychiatry had not met the earlier challenges fully and gradually began to feel isolated. The dawn of a more concentrated effort at social and community psychiatry had been encouraged by Meyer himself. Most important, Meyer had directly and indirectly supported the development of psychoanalysis in the United States; but by the early 1950s psychoanalysis superseded psychobiology and in fact paid only cursory attention to it.

In some quarters (Sargant [10] in the United Kingdom, among others) it was believed that psychoanalysis had taken over United States psychiatry lock, stock, and barrel. This perception was incorrect because, in fact, it overlooked competing ideologies (e.g., in social and biological psychiatry) that frequently challenged psychoanalysis, adding to the siege mentality that consistently pervaded the field. Nevertheless, psychoanalysis developed enormous academic institutional power and affected significant hospitals, associations, and their leaders. Equally, perhaps even more important, ideas and practices throughout the field were profoundly influenced. Repeatedly, I have emphasized one change that is only beginning to be understood by decision makers. Psychoanalysis altered the boundaries of psychiatry radically in terms of its implicit definition of psychopathology and its implicit concepts of what psychiatrists should do and should not do. Freud's *Psychopathology of Everyday Life* (11), in the context of his brilliantly written clinical examples and structural concepts, led to an assumption of the near universality of psychopathology. When psychoanalytic theory was coupled with equally profound changes in child and adolescent psychiatry, the world of nosology was given a near-mortal wound.

In previous publications, I have described these events in detail; in this paper I wish to emphasize a few salient points. Psychoanalysts and psychiatric leaders influenced significantly by analysis failed to perceive the enormous policy influence exerted by psychoanalytic theory and practice. With only rare exceptions, they did not demonstrate an interest in these implications. Epidemiology was essentially ignored as much as nosology, although without the opprobrium that many analysts cast upon classificatory systems. While some psychoanalysts manifested interest in treatment of psychotic patients (and some hospitals demonstrated special interest in psychotherapeutic work with severely ill

populations), the predominant interest shifted away from the severely ill patient.

Furthermore, the overwhelming majority of psychoanalysts demonstrated minimal interest in exploring the relationship between intrapsychic process and new biological concepts. Fixated on hydraulic physical models of energy distribution and mechanics, relatively few analysts became involved in transactional systems, cybernetics, or new systematized field models. For all the neglect of modern biological psychiatry, the attitudes of analysts toward social and community psychiatry were even more negative. In contrast to Meyer's reaching out to develop new community approaches, the dominant pattern of psychoanalysts involved reiteration of the intrapsychic as much more significant than the interpersonal or the social interactional field. To be involved in social psychiatry was seen as diluting the basic concentration.

Increasingly, psychoanalysts manifested a dominant ideological approach based on deductions, belief systems, and therapeutic values. To a significant extent, these patterns related to a need to defend against critics of psychoanalysis. Simultaneously and, in part, reactively, biological and social psychiatry developed their own ideological systems which differed markedly with each other and with analysis. In turn, psychoanalysts surrounded themselves with siege wagons even during a phase when many outside the wagons thought that the analysts held the real power. There is, of course, much truth in the analysts' belief that they were, at best, ambivalently received by colleagues in psychiatry. Nevertheless, the proclivity to be a besieged minority cannot be entirely explained by external attack. It was ingrained into the core functions and psychological structure of many analysts.

By the middle 1960s, American psychiatry was characterized by multiple ideological divisions in which little communication occurred between or among the various groups. While the biological psychiatrists tried to cling to their medical roots, they often became rigid in this defense and were not very persuasive. Limited as they were to unspecific medications and such treatments as ECT, insulin, and even lobotomy, they often found themselves regarded poorly within their profession and by the public at large. The psychoanalysts and the social psychiatrists, on the other hand—each in their own fashion—moved away from a medical model. Their demonstration of only minimal interest in systematic, empirically based etiology, nosology, and epidemiology and in development of treatments based on nosology marked the nadir of psychiatrists' demedicalization in the United States. Simultaneously, it also marked a period of massive public confusion about the differences among clinical psychologists, psychiatric social workers, and psychiatrists. The key paradigm here is that the broader the boundaries of psychiatry and the broader the definition of what a psychiatrist can and should do, the more overlap there is, for example, between clinical psychology and psychiatry. While the emphasis here is on the impact of

boundary problems upon differentiation of mental health professionals, many other factors contributed to role blurring. The shortage of psychiatrists in World War II and in the postwar period led many within psychiatry and outside the profession to support treatment roles of other disciplines.

During the 1950s and most of the 1960s, public demand for psychiatry's accountability had been slow in developing. (Of course, there were many countertrends and exceptions.) Gradually, however, warning signals began to appear on the horizon. While Bailey's scholarly but tendentious critique of psychoanalysis at our 112th annual meeting in 1956 (12) was offset by Ernest Jones's equally eloquent statement at the same meeting (13), the drumbeat of criticism began to mount a decade later. By the late 1960s, a confluence of trends became clear. The combination of psychiatry's boundary expansion, the predominance of ideology over science, and the field's demedicalization began to produce a vulnerability. Many decision makers became skeptical about psychiatrists' capacity to diagnose and treat patients. Criticism of psychiatry began to mount to a level beyond general criticism of weaknesses in medicine as a whole. A new form of stigmatization of psychiatrists gradually emerged. When these developments were perceived in the face of the continuing "shame of the states" (14) and psychiatry's relatively low status in medical schools, and with little demonstration of accountability, a crack in important segments of public support began to widen.

Simultaneously, criticism of institutionalization of psychiatric patients began to reach a zenith. Civil rights activists pointed out that patients had often been hospitalized without sufficient guarantee against abuse. Commitment procedures began to be altered, and a massive movement toward deinstitutionalization began. With the introduction of new psychotropic medication, deinstitutionalization accelerated rapidly. It was hoped that community mental health centers (CMHCs) would meet the needs of their patients, and the legislation developing these centers became a focal point for development in the 1960s. In retrospect, the resources for these centers were not adequate; furthermore, the centers did not concentrate their efforts sufficiently on severely ill individuals.

Superimposed upon deinstitutionalization, revolutionary changes in payment for all medical services had an early impact on psychiatry, given the continuing stigmatization of patients and practitioners. A demand for cost-effective services based on objective data increased steadily. Justification for increased manpower production became required. With the expansion of CMHCs and economic constraints, competition between and among mental health practitioners emerged as a publicly visible reality. The torrid relationship between psychiatry and psychoanalysis started to cool. More and more decision makers and payers of psychiatric services began to visualize the field as a bottomless pit requiring unlimited resources. Steadily, regulation began to replace the free market, and the cottage

industry proved inadequate to meet the new regulatory and economic challenges. By 1970, the critics were joined by those who perceived previous promissory notes, including those made for CMHCs, as having been unmet. We found ourselves caught in the vortex of a crisis. We had difficulty in coping with the new economics, and the bottomless pit was sucking us in.

THE CURRENT SURGE OF NEUROSCIENCE AND PSYCHOPHARMACOLOGY ALONG WITH EMPIRICISM AND LOGICAL POSITIVISM

Biological psychiatry had become isolated in the decade after World War II and had retreated into ideological sparring with the psychotherapeutic boom of the 1950s. Nevertheless, a rising from the ashes was reflected in the clinical trials of chlorpromazine. Practical use of psychotropics soon emerged, and while resistance to pharmacotherapy was distinct in the 1950s, the dawn of the next turning point was strongly influenced by the new science and the new economics. In other presentations, I have emphasized the interaction between the two; some preferred to pay attention to only the science, while others paid attention to the economics (15). The profession must be mindful of both, including their interdependence.

During the past two decades, research in the neurosciences has advanced at a dizzying pace. (It has been especially dizzying to older practitioners whose world seemed to be so markedly changed.) While the advances have affected many medical specialties, the impact on psychiatry had been prodigious. For the scientists working in the laboratories and for many of those engaged in clinical research, the new knowledge emerged because of the freedom of scientists to develop their own hypotheses and to test them objectively. From my perception, social, political, and especially economic forces have also played a critical role in the new research developments. Decision makers on Senate and House appropriation committees have commented frequently that they are now more willing to support the Institutes of the Alcohol, Drug Abuse, and Mental Health Administration because they can understand the palpable outcomes of the new generation of research. The development of public support groups has had enormous significance in accelerating the momentum. The National Alliance for the Mentally Ill has grown rapidly in size and power; its passionate espousal of biological psychiatry will be of great interest to psychiatric historians in the next century. The families of severely ill mental patients, rightly or wrongly, felt attacked by psychotherapeutic and sociotherapeutic concepts in psychiatry. To the extent that genetic, biological variables became preemptive etiologically, the families' poignant struggles to deal with severely ill family members became more easily explainable. The support of the National Alliance for the Mentally Ill for research helped to reinvigorate the National Mental Health Association and facilitated the

formation of disease oriented advocacy groups that demanded advances in treatment of manic-depressive illnesses, phobias (and panic disorders), obsessive-compulsive neuroses, Alzheimer's disease, schizophrenia, and other psychiatric disorders.

Before this late-century turning point, the public image of psychiatry had begun to sour. Public perceptions of the field have always included gross stigmata, but in the heady post-World War II decade, a window of opportunity developed. For me, Ingrid Bergman's portrayal of the psychiatrist in the movie "Spellbound" symbolized a willingness to perceive that psychiatrists could be helpful under most difficult circumstances. At the opposite extreme, Michael Caine's more recent portrayal of the psychiatrist as psychotic murderer in "Dressed to Kill" reflected a composite of negative stigmatized perceptions. The public's negative perception of psychiatry also was a response to unmet expectations, anger at purported abuse of patients, and ridicule of psychiatrists arguing with each other in the courtroom. The reaction to John Hinckley's being determined not guilty by virtue of insanity symbolized the vulnerability of psychiatry far beyond the courtroom. The national firestorm after the Hinckley decision traduced our diagnostic capacities, treatment techniques, and basic competence in every other way. The need to answer these criticisms has affected our policies more forcefully than many of us realize.

During this past decade, the best stories about psychiatry in print and electronic media have involved the scientific advances in the field. As these stories have increased, they have begun to offset the continuing negative stories and may be moving to a point where they will go beyond offsetting. The need to change the public image of psychiatry has also played a key role in producing the current turning point. For some of my research colleagues, this effect is passionately denied as if it meant that their work is designed to influence the public. Just the opposite is true; high-quality work affects the public because it is high quality. But we must want to seek public support while reducing the stigma against patients and practitioners. In this process, a tendency to overcorrect for previous errors is inevitable. A focus upon genetic markers for manic-depressive illness gets much more attention than stories about the less fashionable reports of successful psychotherapy. This attention and the resultant allocation of resources affect many segments of our training programs, certification procedures, and accreditation processes. The overreaction certainly has many practical consequences.

One of the best symbols of late-century American psychiatry has been the increasing centrality of nosology in our scientific and clinical work. From the depths of the 1950s when nosology was perceived by many as an esoteric nonentity, DSM-III and DSM-III-R have influenced American psychiatry profoundly, but they have also been influenced by forces outside the field. By the middle 1970s, key decision makers not only perceived psychiatry as a bottomless pit but also began to

take steps to limit reimbursement for psychiatric treatment. Publicity about psychiatrists testifying on opposite sides of insanity defense pleas brought out enormous criticism about the unreliability of psychiatric diagnosis. By the time of the Hinckley decision, the peak criticism of psychiatry occurred. By then, however, countermoves had already commenced. The nosologists who had created *DSM-III* attempted to shield themselves from political forces, although they could not maintain this stance consistently, and they were simultaneously criticized by social activists (concerning sexism and racism) and by other scientists. Despite this sniping, the *DSM-III* committees and task forces of APA produced amazing documents that did indeed change the shape of American psychiatry. While it was a brilliant tour de force, its acceptance was deeply influenced by the dire need for objectification in American psychiatry. We needed to prove to many people that psychiatric disorders could be diagnosed and that a rational basis for determining how to deal with psychiatric patients could be developed. Thus, there has been great pressure to follow *DSM-III* with treatment guidelines—objective guidelines for when hospitalization becomes necessary and for how long we need to keep people in the hospital. Quantification and objectification moved rapidly, perhaps at times too rapidly, across our entire field. Implicitly, theory building receded and an effort was made to move toward an empirical, quantitative direction where logical positivism and its empirical modes prevailed. Precise thinking could only be said to occur when we used our sensory capacities to observe and measure objectifiable data. This position has been extremely helpful in obtaining research funding and has been adaptive in work with industry and their insurance carriers.

Simultaneous with these sweeping changes, a number of other related developments have occurred. Epidemiology has also moved to center stage from its earlier isolation. The need to collect broad population data to aid in the formulation of psychiatric policies has become obvious. The universality of psychopathology hypothesis extant in Freud's *Psychopathology of Everyday Life* (11) or in Erikson's normal late adolescent crisis (16) could not be afforded—even in affluent America.

The nadir of demedicalization of American psychiatry of the mid-1960s is about to be replaced in the early 1990s by an apogee of remedicalization. It is a structural remedicalization manifested by the emphasis upon etiology, diagnosis, rational choices of treatment, psychobiological approaches to prevention, and the importance of epidemiology. It also is reflected in psychiatry's alliance with other medical specialties and medical organizations.

In this context, the borders and boundaries of psychiatry that seemed infinite in the 1960s became somewhat narrower; we promised much less to be all things to all people and we limited both our declared areas of expertise and our definitions of disorder.

In the 1960s, our field had been dominated by

boundary expansion and by predominance of ideology over science and demedicalization. By 1989, our field is dominated by a remedicalization, a predominance of science over ideology, and a tendency toward boundary circumscription. While *DSM-III* and *DSM-III-R* are still very broad in scope, they attempt to provide objective criteria for diagnosing each disorder. Psychiatrists have also tended to focus much more on clearly defined role functions than they assumed in the 1960s. Explicit and implicit action was taken to respond to those critics who had described psychiatry as a bottomless pit in the 1960s. Nevertheless, there are signs that the remarkable correction that has taken place in the last two decades has overcorrected in some areas. Fears of losing vitality in clinical psychiatry have been expressed by an increasing number of observers. Caricatures of a "mindless" psychiatry (17) have replaced the previous "brainless" psychiatry and are drawing increased attention. I believe that these forces and others will begin to combine at the beginning of the next century and I will conclude this paper by predicting another turning point by the first decade of the twenty-first century.

THE REEMERGENCE OF ANALOGUES OF MEYERIAN PSYCHOBIOLOGY AT THE TURN OF THE TWENTY-FIRST CENTURY: A PREDICTION

The point and counterpoint of current American psychiatry include predecessors of changes that I believe will gather momentum to become the next turning point. Rutter (3) has pointed out frequently that we must study the large population who do not become ill when facing the genetic and life-stress factors that induce illnesses in so many others. Along with a number of distinguished observers, he has emphasized the remarkable individual variations in coping with high-risk variables. Meyer had discussed this phenomenon on many occasions, and leaders of psychosomatic medicine have repeatedly called attention to such variations. While these questions have been given attention, I believe that a confluence of factors will elevate the questions about adaptation and coping to a pivotal position in psychiatry.

To predict that issues which have been in the penumbra of psychiatry for over a century will move to center stage may be risky, but I do believe that there are good reasons to make this prediction. By the beginning of the twenty-first century, I believe that the adaptability of many individuals with apparent high-risk loading for psychiatric illness will not be able to be ignored. In addition to scientific development, I believe that economic forces will be at play and policy makers will want to know why large segments of the population fail to become ill. The capacity to cope and hence to reduce risk of illness will be very important in the actuarial world of the early twenty-first century.

Simultaneously, the technological advances of the late twentieth century will be applied to determine

markers of adaptability just as we now study markers of disease proclivity. When our technology permits longitudinal studies of biological systems and adaptability, we will be in an advantageous position for new hypotheses. In effect, I am saying that the psychobiology of coping and adaptability will become a major part of psychiatric research and practice. Modern technology will permit us to take Meyer's old concepts and apply them (as well as the best of psychosomatic medicine) in a variety of new ways. Integral to this new emphasis will be the transactions and interactions between psychological adaptation and biological systems. Both pathology and health will need to be explained in psychobiological terms.

The increased interest in adaptation could have a direct influence on the clinical practice of psychiatry in the early part of the twenty-first century. At present, there is a decline in interest in taking a full psychiatric history; establishing criteria for a *DSM-III* diagnosis has become the current cornerstone of psychiatric history taking. With a decline in psychodynamic formulations, the excitement in looking for historical and other clinical nuances has almost been lost. Many clinician educators have talked about loss of clinical vitality in the profession. I am convinced that revived interest in adaptation could help to reverse this trend. Currently, axes IV and V of the *DSM* are primarily research tools, but I believe that scientific and economic forces will increase our attention to the field of stress and adaptation. To the extent that clinicians as well as researchers see the value in documenting these data, collecting and interpreting such information will become a major part of day-to-day clinical practice. I am hopeful that the process of collecting such data will stimulate a new interest in history taking. The psychodynamic formulation of the 1950s might be replaced by a psychobiological (or biopsychosocial) formulation of the year 2010. This formulation will involve more than historical data, since laboratory findings (measuring both adaptational and pathological elements) should also become very important.

For many years I have been interested in psychiatrists' involvement in research on normal populations (18, 19). In part, this interest has been based on a wish to find empirical bases to distinguish normal from pathological conditions in psychiatry. I am convinced that such efforts will ultimately help to define the scope and boundaries of psychiatry. There is every reason to believe in much greater variety of normal development than there is in pathological sequences. Longitudinal studies of life-course adaptation will catalyze our knowledge in this arena, and I look forward to exciting progress that will attract the next generation of investigators and clinicians. As I have studied Meyer's efforts in history taking, he was seeking a way to follow "persons" (to use his term) throughout successive developmental stages, but he lacked the tools and measurements to make it practical. His vision on this matter, however, deserves to be studied in preparation for a new kind of history taking that will seek to ascertain both adaptational and pathological elements.

With increased emphasis upon coping, the boundaries between health and illness, and life histories, I believe that the clinical psychiatry of the early twenty-first century can be revitalized without becoming vitalistic. The new clinical psychiatry can lift us from the potential reductionism, mechanization, and trivialization that weaken current clinical psychiatry. It can also keep open lines to develop new hypotheses rather than seeking dynamic formulations that follow established theoretical constructs.

The revitalization of clinical psychiatry should also permit us to find a new synthesis of psychoanalytic, social psychiatric, and biological psychiatry. In the years after World War II, American psychiatry has oscillated widely between dominant concepts and practices. A more steady, empirically driven phase should modulate and temper the current overcorrection. As the tempering occurs, new ideas about comorbidity and multimodal treatment should develop. Indeed, I anticipate that most psychiatric patients early in the next century will be treated by combinations of psychotherapy and somatic therapies. These combinations will be based on empirical clinical trials, and a generation of clinician-educators experienced in such combinations will become the modal supervisors and textbook writers.

My predictions are based on both scientific and economic indicators. I am, of course, hopeful that leaders in psychiatry will see the new opportunities in the next phase. I am also hopeful that decision makers and the general public will support these efforts.

Adolf Meyer was not born in the United States, but he helped to create an indigenous psychiatry, the first American psychiatry since the moral reform period early in the nineteenth century. After the turbulence of the last half of the twentieth century, we may have an opportunity to reflect on what Meyer accomplished and find a new balance. We can build on his base but we must also take advantage of new technology, new methods, new public support, and new partnerships with patients and their families to facilitate and support the next turning point.

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Evidence of the Role of Psychosocial Factors
in Diabetes Mellitus: A Review

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Diabetes mellitus is a very prevalent illness that produces a variety of stresses for the individual patient, but the role of psychosocial factors in this illness is frequently minimized in the teaching of physicians and the care of patients. The authors review a framework for evaluating the role of psychosocial issues in illness in general and examine the evidence that demonstrates the importance of these issues in diabetes.
(Am J Psychiatry 1990; 147:1275–1282)

The role of psychosocial factors in diabetes mellitus has long been a controversial topic. Investigators at one extreme believe in a causal role of psychosocial factors even in the onset of illness, and those at the other extreme believe that psychosocial factors play a minimal role in comparison to physical management of the illness. Individual patients often ascribe a very major role to emotional status (1), but demonstrating this role in well-controlled studies has been quite difficult. There has been an unfortunate tendency in some medical circles to minimize psychological factors, thus depriving patients of a comprehensive approach to their problems. In this paper, we will review from several different perspectives evidence that points to a very vital role for emotions in the course of diabetes.

In looking at the work that has been done, we will follow the outline recommended by Stevenson and Graham (2) and expanded by one of us (3), which examines evidence from six different perspectives to determine the role of psychosocial factors in precipitating a disease or affecting its course. 1) Anecdotal case reports and personality studies look at the influence of psychosocial factors on the course of the disease in individual patients. 2) Epidemiologic studies can demonstrate the relationship between the severity of the disorder and varying degrees of psychosocial stress experienced by different population groups. 3) Studies of both overall concordance rates and careful clinical studies of discordant pairs of twins help sort out constitutional from emotional factors. 4) The physiological effect of artificially induced stress on subjects with the disease can be measured. 5) The effect of emotions on the disease process can be demonstrated by evaluating the effect of psychosocial interventions, including psychotherapy and psychoactive medications, on the disease. 6) Basic science investigations of human response to stress and of animal models of the illness can elucidate mechanisms in a clearer way than can clinical studies. As we will show, all of these approaches have been used to gain a better understanding of how psychosocial factors play an etiological role in the course of diabetes mellitus.

ANECDOTAL CASE REPORTS

Anecdotal case reports abound in the literature as well as in most of our practices. Menninger (4) described a number of patients who developed glycosuria during a period of emotional upheaval, which remitted with psychotherapeutic treatment. Hinkle et al. (5, 6) closely followed a number of patients with either insulin-dependent or non-insulin-dependent diabetes and found a close link between psychosocial stressors and the onset and course of illness. A more recent report (7) described the development of transient non-insulin-dependent diabetes in a Korean physician in the course of his immigration to the United States. Psychological issues for this individual included culture shock compounded by marked distress regarding separation from his family. Although there are many dramatic reports, this evidence is criticized as too uncontrolled to demonstrate the etiological role of psychosocial factors in the course of disease.

PERSONALITY FACTORS

As a corollary of the individual case studies, investigators have asked if there are particular personality factors that affect the onset or course of illness. This approach was described by Florence Dunbar et al. (8) in 1936 and Franz Alexander (9) in 1950. They looked for particular personality types or unconscious conflicts in patients with given illnesses. In diabetic patients they found a preoccupation with oral issues. The

problem with such studies is that the investigators typically fail to differentiate the effects of the disease itself from preexisting characteristics. Clearly, some of the personality attributes could be an effect of genetic characteristics of diabetic patients or an outcome of months and years of experience with a disabling illness.

A more illuminating approach to personality characteristics was that of Stabler et al. (10), who studied the effect of type A versus type B personality characteristics on the disease process in diabetic children. Through the children's responses to video games, the experimenters were able to identify diabetic children as having characteristics of type A or type B personality. They found that children with type A personalities had a hyperglycemic response to stress that was not present in the children with type B personalities. Such results strongly suggest that an individual's personality characteristics can affect glucose regulation.

Other studies (11–13) have focused on ego development or particular personality traits, such as self-esteem and locus of control, and have found positive correlations with these traits and control of the illness. Related to personality studies are studies of the prevalence of psychiatric diagnoses in diabetic patients. Popkin et al. (14) studied 75 patients undergoing evaluation for pancreatic transplantation and found one or more psychiatric diagnoses in half of the patients and a lifetime prevalence of major depression in one-quarter. Although earlier claims about the existence of a diabetic personality have not been corroborated, personality characteristics are clearly important, and psychiatric disorders are underdiagnosed in diabetic patients.

EPIDEMIOLOGIC STUDIES

Epidemiologic studies of psychosocial stress in the pathogenesis of disease typically look at the importance of psychosocial variables by studying the association of these variables with the disease process in different groups of patients. They ask, To what extent do we find a greater number of psychosocial stresses such as losses or disturbed family situations preceding the onset of diabetes? How do those patients with psychiatric symptoms deal with the disease in comparison with those who do not have such symptoms? What are the psychosocial correlates of good versus poor control of the illness?

Early researchers (15, 16) found a correlation between stressful life events, particularly losses, and onset of diabetes, but the studies did not provide adequate controls. Stein and Charles (17) attempted a more controlled study by comparing 38 diabetic adolescents matched with 38 patients with other chronic illnesses and found a predominance of parental loss and severe family disturbance in the diabetic group; 77% of these losses preceded the onset of diabetes. Robinson and Fuller (18) examined the role of stressful life events in the onset of diabetes by comparing diabetic patients with their siblings and with neighborhood matched control subjects and found much greater numbers of stressful life events in the patients than in the two control groups. Although studies of life events are subject to recall bias and problems with weighing the importance of a stress, they have provided evidence suggesting a role for emotional factors in the onset of diabetes.

More recent studies evaluating the relationship between psychosocial factors and control of diabetes have benefited from the ability to measure glycosylated hemoglobin, which provides an objective measure of diabetic control over the previous 4–6 weeks (19). In a study designed to examine the relationship between psychiatric problems and such control, Lustman et al. (20) used a structured interview and the Hopkins Symptom Checklist to determine the prevalence of psychiatric diagnoses to study 114 randomly selected diabetic patients. They compared these data with data on diabetic control as measured by glycosylated hemoglobin and found significantly worse diabetic control in patients who had a history of psychiatric illness than in those who had none (glycosylated hemoglobin values of 9.6% versus 10.5%; a value greater than 10% is indicative of poor control). Although a clear conclusion from this study is that psychiatric symptoms are correlated with poorer control, the possible explanations are numerous: psychiatric problems lead physiologically to poorer control, psychiatrically disturbed patients exhibit poor compliance, or the psychiatric symptoms result from poor diabetic control directly or as an effect of the physiology of poor control. Although the study of Lustman et al. cannot definitively establish which of these possibilities are true, the fact that psychiatric illness preceded recognition of diabetes in 94% of the 34 psychiatrically ill patients studied makes it unlikely that the findings were merely a result of the subjects' having the illness.

Another study correlating emotional factors with diabetic control as indicated by glycosylated hemoglobin is that of Peyrot and McMurry (21). They studied 20 insulin-dependent adult diabetic patients and their spouses through interviews and questionnaires administered in their homes. Peyrot and McMurry found significant differences between patients in good and poor control on a number of psychological dimensions, leading them to conclude that psychological adjustment "affects control through both behavioral and psychophysiological mechanisms" (p. 553). Schwartz et al. (22) found that recent life events in 19 diabetic patients were correlated with poorer control as measured by glycosylated hemoglobin; interestingly, good social support was found to buffer this effect somewhat.

There are many studies exploring the importance of psychosocial variables in diabetes in children and adolescents. Johnson (23) provided a comprehensive review of studies up to 1979 and an excellent discussion of their methodological limitations. A particularly comprehensive study by Fallstrom (24) included all the diabetic children in a Swedish community. These chil-

dren and a group of nondiabetic control children were studied with interviews, psychological testing, and EEGs. The diabetic children showed more body image abnormalities, more problems with school and peers, and a higher percentage of neurological findings.

Swift et al. (25) studied 50 juvenile diabetic patients and 50 individually matched control subjects and found significantly more psychopathology in the diabetic patients. Simonds (26, 27) studied 40 diabetic boys in good control and compared them with 40 boys in poor control and 40 subjects without diabetes. Although he found correlations between psychological distress and poorer glucose control, here again it was not possible to conclude whether the psychological distress was a cause or effect of the poor control. Another study by Simonds et al. (28) failed to show a correlation between psychological variables and glycosylated hemoglobin levels, but this study depended largely on self-report scales, a method that is subject to the motivation and honesty of the subjects.

Grey et al. (29) administered a number of psychological scales to 20 latency-aged diabetic patients in their homes. Fifty-five percent of these patients fell into the category of moderate to severe psychosocial maladjustment according to the authors' measures, and when they compared these children with diabetic patients who appeared not to be disturbed, they found that the 24-hour urine glucose excretion of the disturbed children was two to three times higher. Another interesting finding in this study is that higher self-esteem in the parents correlated very strongly with good diabetic control in their children. Bobrow et al. (30) studied 50 adolescent girls with insulin-dependent diabetes and their mothers and found a correlation between conflict in the mother-daughter dyad and poor adherence to the medical regimen. Many researchers (21, 25, 27) have found that adolescent girls have more difficulty maintaining diabetic control than other groups, as evidenced by glycosylated hemoglobin. It may be that the earlier maturation of girls plus the special conflicts in the mother-daughter relationship sensitizes them to issues related to their illness. It has also been speculated that physiological changes associated with puberty may result in poorer diabetic control.

Many of the studies cited have shown a relationship between psychological variables and metabolic control, but they have not been able to differentiate whether their findings indicate that underlying psychosocial problems have a causal role or that these problems are simply effects of varying levels of severity of the illness. They have also not been able to determine whether, if there is a causal relationship, the linkage occurs through compliance or some unspecified neuroendocrine effect. In a more recent study, Jacobson et al. (31) studied 57 children with recent onset of diabetes. These investigators applied measures of personality variables and compliance and followed the children for 18 months. They found that "initial patient reports of self-esteem, perceived competence, social

functioning, behavioral symptoms and adjustment to diabetes predicted subsequent compliance behaviors." The fact that psychological factors detected at the outset of the disease predicted compliance in these patients provides stronger evidence for the causal role of these factors.

In a well-controlled study, Delamater et al. (32) studied groups of diabetic adolescents in good, fair, or poor control to determine whether measures of anxiety, stress, and means of coping with stress varied among the groups. Subjects were matched for age, disease duration, and socioeconomic status, and their levels of control were determined by glycosylated hemoglobin measurements. Delamater et al. found that the subjects in good control reported more academic stress and the subjects in poor control reported more stress related to diabetes. What was particularly important was their finding that the subjects' modes of dealing with stress were quite different: those in poor control used significantly more wishful thinking and avoidance than those in better control. These authors did not find a relationship between stress and metabolic control, perhaps because the scales they used were unable to detect some of the disease-related stress of diabetic adolescents.

Although many studies have shown a link between stress and metabolic control, for the most part it has not been possible to show whether stress affects metabolic control directly or exerts its effect by influencing compliance. In a study designed to investigate this question, Hanson et al. (33) obtained extensive measures of metabolic control, compliance behaviors, stress, social competence, and parental support for 104 adolescents with insulin-dependent diabetes and their mothers. Using multiple regression analysis, Hanson et al. found that stress had a direct effect on metabolic control when the effect of compliance was controlled. They also found that the effect of stress was greatly buffered by social competence; subjects scoring high on social competence had minimal changes in glycosylated hemoglobin in response to stress, but those with low social competence had marked worsening of values. These results also highlight the complexity of detecting the effect of stress on diabetes; if Hanson et al. had not had the number of subjects they did and had not separated patients according to social competence, their findings would have been far less significant. Linn et al. (34) have also shown that stress affects glycemic control apart from its effect on compliance in a longitudinal study of the effect of stressful life events on immune functioning in 20 patients with insulin-dependent diabetes, 20 patients with non-insulin-dependent diabetes, and 20 healthy control subjects.

Studies of patients with brittle diabetes typically demonstrate a close link between psychosocial factors and diabetic control. Orr et al. (35) studied 15 adolescents with poorly controlled diabetes and found a high incidence of family problems and psychosocial problems, including excessive school absence, depression, and social isolation. They also found surreptitious in-

sulin administration (36) in six of these patients, typically in the context of psychiatric problems such as depression; two of the patients used insulin in suicide attempts. In another study of 33 patients with brittle diabetes, Gill et al. (37) attributed poor control to psychological reasons in one-third of the patients; one patient was found to have factitious hypoglycemia. Half of the patients in whom no reason for brittle diabetes could initially be found were later found to be interfering in some way with their diabetic treatment.

In a study of 30 patients, Schade et al. (38) found that eight had factitious disease, eight were malingering, and seven had communicative disorders, deficits in information processing that became apparent only after extensive psycholinguistic testing. White et al. (39) retrospectively studied 30 children and adolescents with unstable diabetes and their families and concluded that most of the instability was not from intercurrent illness but from emotional stress, sometimes working synergistically with poor compliance in families with limited problem-solving skills.

To summarize the findings of epidemiologic studies and other group comparisons, correlations have long been found between psychosocial variables and diabetic control, but earlier studies were less able to separate cause and effect. As studies have become larger and better controlled, they point more clearly to an etiological role for psychosocial variables in the illness, not only through impaired compliance to treatment regimens but also as a more direct neuroendocrine effect of stress.

TWIN STUDIES

Studies of twins discordant for a specific disorder may help to discover environmental factors that affect disease onset and degree of morbidity. Barnett et al. (40) studied 200 pairs of twins with diabetes and found concordance rates of 54% in twins with insulin-dependent diabetes and 91% in twins with non-insulin-dependent diabetes. From these and other studies, it is clear that genetic factors play a very strong role in onset of non-insulin-dependent diabetes but a lesser role in insulin-dependent diabetes. Another fact revealed by the study of Barnett et al. was that in middle life (ages 20 to 39 years), most of the pairs discordant for insulin-dependent diabetes lived apart, whereas only half of the concordant pairs did, suggesting the possibility of a shared environmental factor. Srikanta et al. (41) studied sets of twins initially discordant for diabetes. One of the initially nondiabetic twins developed islet cell antibodies 5 years before the onset of diabetes, suggesting that precipitating factors of the illness can precede the onset of illness by many years. Heaton et al. (42) studied the identical twins of 10 patients with insulin-dependent diabetes who had not developed the disease for more than 11 years and thus were unlikely to develop diabetes. These subjects had normal glucose tolerance but greater insulin secretion,

suggesting dysfunction of the beta cells of the pancreas that did not lead to clinical diabetes. We wonder what factors led to different outcomes in these identical twins.

Unfortunately, none of the major studies of twins discussed the possible role of psychological factors in the discordance. A report by Loeb et al. (43) provided biographical data about one pair of identical twins discordant for non-insulin-dependent diabetes. One twin developed diabetes and major depression late in life, but the other developed coronary disease and anxiety. Differences in their psychological coping mechanisms could be traced to early life experiences; the diabetic twin tended to be more compulsive and depression-prone whereas the nondiabetic twin tended to repress his anxieties and deal with stress by activity. This study of the interaction of developmental factors with subsequent expression of disease in individuals with identical genetic makeup provides fascinating material for consideration of the mind-body interaction. Its significance regarding discordant twins is limited, however, since the fact that there was apparently no follow-up and no glucose tolerance testing of the discordant twin suggests the possibility that the pair will not remain discordant. More psychiatric studies of discordant twin pairs would be useful to examine the role of psychosocial factors in the pathogenesis of disease.

ARTIFICIALLY INDUCED STRESS

To have a more controlled situation than is possible in the type of studies already described, researchers have used artificially induced stress to assess the effect of stress on glucose regulation. Hinkle et al. (6, 44, 45), early researchers in this area, induced stress in some of their patients and found changes in their blood ketone levels that remitted when the stress was removed. Vandenbergh et al. (46) studied the effect of hypnotically induced stress on six diabetic patients, four with brittle diabetes and two with mature-onset diabetes. When patients were submitted to personalized stress under hypnosis, there was an increase in free fatty acids but no increase in serum glucose. It seems likely that the effect of the hypnosis itself probably outweighed any possible hyperglycemic effect of stress.

In a more recent study, Kemmer et al. (47) tested whether stress would affect glucose control in patients with insulin-dependent diabetes. Using the experimentally induced stresses of public speaking and mental arithmetic and measuring changes in the counterregulatory hormones, Kemmer et al. found that this short-lived stress raised cortisol levels but did not lead to changes in levels of glucose, ketones, free fatty acids, glucagon, or growth hormone (GH). Although some physicians have been tempted to make far-reaching conclusions from this study, all that was proved, as the authors stated, was that short-lived experimentally produced stress does not affect glucose control in patients with insulin-dependent diabetes. The type of

emotional stress that has typically been correlated with poor control is more chronic and much more personally meaningful (e.g., being told of impending blindness). Studies of artificially induced stress have limited utility in understanding the impact of psychosocial factors on diabetic patients.

PSYCHOSOCIAL INTERVENTIONS

Studies of the effects of psychosocial interventions include the effects of ECT, psychotropic medications, and various forms of psychotherapy, including relaxation, biofeedback, and family therapy. ECT has been shown to lower blood glucose in some depressed diabetic patients (48), perhaps by its action on reducing the elevated ACTH and cortisol levels found in depression. This finding is consistent with other reports suggesting that diabetic control worsens with depression and improves with antidepressant treatment (49).

There are several reports that individual psychotherapy with diabetic patients has a favorable effect on control. One of us (50) described a successful psychotherapeutic intervention for a 43-year-old woman with insulin-resistant diabetes requiring more than 300 units of insulin per day. After a 2-week course of psychotherapy conducted on a clinical research unit focusing on the patient's concern about her daughter's ill health, she returned to her previous requirement of 30 units of insulin per day. Several others (35, 51, 52) have reported successful use of individual psychotherapy for patients with recurrent ketoacidosis. Group therapy has a particularly important place in providing peer support in work with adolescents, who traditionally show deteriorating compliance. Warren-Boulton et al. (53) reported on one such group and found improvement in the individual patient's compliance and glycemic control over an 18-month period.

Physiological observations in patients with ketoacidosis have shown major elevations in plasma glucocorticoids, GH, and glucagon concentrations as well as in urinary excretion of epinephrine and norepinephrine (54). Many investigators feel that these counterregulatory hormones play a major role in the development of ketoacidosis during stress, whether the stress is physical, such as an infection, or emotional. Applying the theory of the role of the sympathetic nervous system in diabetic ketoacidosis, Baker et al. (55) administered propranolol to two girls with diabetes who had been incapacitated with recurrent admissions for diabetic ketoacidosis; the girls experienced a dramatic reduction in the frequency of their hospitalizations. Biochemical studies have demonstrated that β-adrenergic blockade could block the increases in plasma levels of cortisol, GH, free fatty acids, and urinary catecholamine excretion otherwise seen in these subjects under stress. Baker's group was working together with Minuchin, and, ultimately, family therapy replaced the use of adrenergic blockade.

Minuchin et al. (56, 57) used therapy with the families of diabetic children who were recurrently hospitalized with ketoacidosis. They found a subset of these patients with numerous admissions that could not be explained on the basis of either infection or poor compliance who were easily controlled when living away from their home environment. They described these patients as "psychosomatic" diabetic patients whose poor control related to a particular family constellation involving enmeshment, rigidity, and lack of conflict resolution. With family therapy, Minuchin et al. were able to eliminate the need for repeated hospitalizations in these patients. Critics (58) charged that Minuchin's group failed to take into account the family disruption caused by unstable diabetes, to which Rosman and Baker (59) replied that the psychosomatic family as they described it is not just lacking in adequate education or support but is experiencing a process that promotes continuation of the illness. Although the work of Minuchin et al. would be enhanced by larger numbers of patients and better controls, it is an important contribution to understanding the impact of family dynamics on neuroendocrine control of the disease process.

Given the clinical data suggesting an association between stress and loss of diabetic control, one would naturally consider testing the effects of stress-reduction techniques, including hypnosis and biofeedback, on disease control. Studies of the effects of stress-reduction techniques (e.g., progressive muscle relaxation and electromyographic biofeedback) in diabetic patients have yielded some conflicting results. Lammers et al. (60) found a positive effect of progressive muscle relaxation in weekly sessions in two out of four outpatients with insulin-dependent diabetes told to practice daily on their own. Landis et al. (61) demonstrated a clinically meaningful decrease in serum glucose levels in four of five patients with insulin-dependent diabetes initially in good control. Feinglos et al. (62) found no improvement in glucose control in response to relaxation therapy in a group of 10 patients with insulin-dependent diabetes who were chosen for poor control and a history of emotional stress affecting their glucose control. The same group (63) found a significant improvement in glucose tolerance in 12 patients with non-insulin-dependent diabetes in response to relaxation therapy. It would appear from these studies that behavioral stress reduction techniques improve diabetic control in certain patients but not in others. The fact that psychosocial interventions can significantly ameliorate glycemic control in some patients provides further evidence of the role of psychosocial factors in the disease process.

BASIC SCIENCE INVESTIGATIONS

Although an extensive description of the possible physiological underpinnings of the CNS control of glucose regulation is beyond the scope of this paper, we will outline several of the areas that are important in

the psychophysiological process. Schade and Eaton (64) conducted a study to determine the role of the counterregulatory hormones in causing metabolic decompensation in patients with insulin-dependent diabetes. The subjects underwent pyrogen stress under conditions that assured adequate insulin levels. Elevated serum levels of glucagon, cortisol, catecholamines, and GH were documented, as were subsequent increases in ketone bodies and blood glucose over the control period. This study helps to support the hypothesis that stress alone, without omission of insulin, can lead to ketoacidosis.

Current theories of the autoimmune basis of insulin-dependent diabetes (65) suggest that the CNS has an important role through its influence on the immune system (66). Somatostatin, which is found throughout the nervous system, counteracts the effects of GH and inhibits glucagon release by the pancreas (67). This process may well be another important link in the effect of stress on diabetes.

There is some evidence that non-insulin-dependent diabetes is a result of an inherited sensitivity to enkephalin, a neurotransmitter that can be affected by stress. Pyke (68) described this hypothesis in connection with Claude Bernard's studies of piqûre diabetes more than a century ago; Bernard produced temporary diabetes in laboratory animals by producing lesions in the floor of the fourth ventricle. Siever and Davis (69) hypothesized that non-insulin-dependent diabetes is a disease of dysregulation of neurotransmitter systems, analogous to depression.

Animal studies shed further light on the interaction of behavioral and environmental issues with glucose control by permitting the use of controls that are more difficult to employ with human subjects. Eigler et al. (70) studied the physiological response of dogs to infusions of physiological doses of glucagon, epinephrine, and cortisol, measuring the resulting levels of glucose and insulin. They found a synergistic response among these hormones; a combination of any two yielded a rise in plasma glucose up to three times as high as the response to the use of one of the hormones singly. They also found that pretreatment with methylprednisolone yielded a much greater response to the counterregulatory hormones. Fujimoto et al. (71) studied the adrenergic mechanisms in the hyperglycemia of genetically diabetic mice and found that these mice had an accentuated response to epinephrine stimulation which could be blocked by propranolol. These findings suggest a parallel with the hyperglycemic response seen clinically when a patient is under emotional stress.

In an experiment showing the effect of environment, Ader et al. (72) studied the effect of different housing conditions on the diabetic response of rats to a dose of alloxan and found that rats raised in groups were more susceptible to the hyperglycemic response than those raised alone. This study suggests that there is a differential response in animals with identical genetic susceptibility on the basis of psychosocial factors. Single versus group housing conditions have been shown to

have a profound impact on the pituitary-adrenal axis in rodents.

Surwit et al. (73) did some interesting conditioning studies in which they compared the glucose response to stress of obese versus lean mice. Obese rats had an exaggerated response to stress that could be ameliorated considerably by treatment with the benzodiazepine alprazolam. Surwit et al. (74) also demonstrated the conditioning of the hyperglycemic response in these mice by pairing stress with a metronome and then producing hyperglycemia with the metronome alone (the conditioned stimulus). These studies demonstrate the importance of stress in the development of a diabetic pattern in genetically predisposed mice. Surwit et al. also showed that a benzodiazepine can modify this response, either by the physiological effect of chemical stress reduction or by some direct action of benzodiazepines on insulin secretion. The fact that a physiological response can be conditioned suggests the possibility of psychosocial cues serving as a stimulus for hyperglycemia. These studies in animals provide further understanding of the role of psychosocial variables in this disease, although caution must be exercised in extrapolating conclusions to human beings. Barglow et al. (75) provided a detailed review and critique regarding the effect of stress on metabolic control in diabetes.

CONCLUSIONS

We have provided an overview of six different research approaches that provide evidence for an important role of psychosocial factors in the precipitation and course of diabetes mellitus. The conflicting results that have been obtained by the investigators are a tribute to the difficulty of unraveling the effects of the disease on psychosocial factors from the effects of psychosocial factors on the disease; they demonstrate the danger of an overreliance on only one or two research approaches. Good psychosocial research requires close attention to how stress is defined, how the patient's clinical history is elicited, and the control subjects selected. The preponderance of evidence described here supports a very important place for psychosocial factors in diabetic control. The role of psychosocial factors in disease onset still remains controversial; long-term prospective studies of individuals at high risk for the disease are needed to provide conclusive evidence.

For the primary care physician, the results of the studies cited point out the need for careful attention to psychosocial factors in the precipitation of the initial onset of diabetes, the precipitation of episodes of ketoacidosis, and the management of the diabetic patient in poor control. The primary care physician needs to consider attention to dietary indiscretion and poor compliance with the use of insulin. In addition, the physician must undertake a search for evidence of psychosocial upheaval and, if this is found, attempt to provide appropriate intervention, possibly through in-

dividual or group psychotherapy or other stress-reduction techniques. Assisting the diabetic patient to cope with the death of a loved one or with marital disruption may help avoid hospitalizations or other difficulties. The physician may chose to undertake the psychosocial intervention directly or may decide to refer the patient for this aspect of care.

For the psychiatrist, the findings cited suggest some useful approaches. For example, in working with diabetic patients who have been referred for depression or other problems, the psychiatrist may be the first to discover a connection between disturbed interpersonal relationships and poor diabetic control. The psychiatrist then has the opportunity not only to intervene appropriately but also to call the primary care physician's attention to a possible causal connection between the patient's dysphoria and poor control of the patient's diabetes.

For researchers, there are several important needs. The presence of only one psychiatric investigation of a discordant twin pair in view of the substantial numbers of discordant twin pairs that apparently exist suggests a promising area for the clinical investigator. Find the discordant twins, document their monozygosity, and then undertake careful life history studies to determine what psychosocial differences, if any, might account for the different experiences with diabetes mellitus.

Perhaps our greatest need is for better controlled clinical trials of psychosocial forms of intervention in patients with diabetes mellitus. Studies of the role of psychotherapy in the management of chronic ulcerative colitis helped to provide convincing corroboration of many clinical observations of the management of individual cases (76). The work of Spiegel et al. (77) in demonstrating the favorable effect of group psychotherapy on the survival rate of patients with breast cancer points out an effective way of efficiently managing treatment resources with a sufficiently large sample of patients to draw meaningful conclusions. These approaches need to be used with groups of diabetic patients.

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Is Locked Seclusion Necessary for Children Under the Age of 14?

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A retrospective study of the effect of the implementation of an unlocked seclusion policy was conducted on three child psychiatric inpatient units in a state hospital in Pennsylvania. Unlocked seclusion was associated with 1) increased use of tranquilizing medications administered as needed on all three units, 2) increased clustering of medications, administered as needed, in the units that used seclusion most, 3) diverse changes in the three units regarding frequency and clustering of unlocked seclusion, and 4) increased correlations between medications administered as needed and seclusion, particularly in the more behaviorally disturbed children. These findings suggest that locked seclusion may be a necessary therapeutic intervention, particularly with severely disturbed children with serious conduct and impulsive disorders.

(Am J Psychiatry 1990; 147:1283–1289)

T he use of seclusion in inpatient child psychiatric facilities remains a complex, controversial, and often misunderstood issue. Gutheil clearly expressed the problems: "Seclusion has been popularly linked to solitary confinement or 'punishment' in a behavior modification paradigm. There are two major sources for this view: seeing seclusion out of context as merely a locked door curtailing freedom, and lack of familiarity with the rationale behind seclusion as a treatment modality, so that one loses sight of its therapeutic purpose" (1).

Several studies have reported on the uses of seclusion in adult psychiatric settings (2–4); however, there are few empirical studies on the use of seclusion with children under the age of 14. The APA Task Force Report on Seclusion and Restraint noted that "indications and procedures for use of seclusion in children are generally identical with those for adults, however much this may surprise the uninitiated. Even seven to ten year old children may require as many as five adults to safely manage them when they are violently out of control" (5).

In Pennsylvania, locked seclusion of children under 14 years of age is currently prohibited by Department of Public Welfare regulation 8488.3.5 (6). This regulation was enforced in January 1987, at which time locking mechanisms were removed from seclusion room doors on the inpatient children's unit at Mayview State Hospital. This retrospective study attempts to examine the clinical impact of the removal of locks from the seclusion room doors.

METHOD

Clinical Setting

The Children's Psychiatric Treatment Center at Mayview State Hospital is a 32-bed unit designed to provide intensive inpatient psychiatric treatment for severely emotionally disturbed children. The center admits patients up to the age of 13 regardless of race, sex, or socioeconomic status and provides comprehensive diagnostic assessment, individual treatment planning, milieu therapy, and individual, family, behavioral, and psychopharmacological intervention when indicated.

TABLE 1. Duration of Seclusion and Daily Number of Patients on Three Child Psychiatric Inpatient Units During Periods With Locked and Unlocked Seclusion

Period	Unit for Older, Emotionally Disturbed Children			Admission Unit			Unit for Younger Children With Conduct Disorders		
	Duration (days)	Patient N		Duration (days)	Patient N		Duration (days)	Patient N	
		Mean	SD		Mean	SD		Mean	SD
1: Locked seclusion	86	10.84	0.4	114	10.02	1.1	142	9.92	0.3
2: Unlocked seclusion	86	10.34	0.8	114	9.93	0.8	142	9.12	1.0
3: Unlocked seclusion and unit privilege behavioral level system	86	11.00	0.0	114	9.66	1.5	142	8.20	1.5

At the time of the study the center was divided into three units that housed both boys and girls. The admission unit, which has 11 beds, served the dual functions of admitting all patients regardless of psychiatric diagnosis and housing those children who continued to display severe oppositional and behavioral management problems. The unit for younger children with conduct disorders was a 10-bed unit that housed children of about ages 6–10 years with behavioral problems in the areas of impulsivity, distractibility, hyperactivity, and oppositional behaviors. The unit for older, emotionally disturbed children was an 11-bed unit for children of about ages 10–13 years who had demonstrated therapeutic gains in their initial treatment and were able to tolerate a less highly structured milieu.

On Jan. 3, 1987, the children's center came into compliance with Department of Public Welfare regulation 8488.3.5. Locking mechanisms were removed from the seclusion room doors on each of the three units during a 2-week period of time, between Dec. 22, 1986, and Jan. 2, 1987. Given the serious nature of the behavioral problems that necessitated the use of seclusion, after the locks were removed from the doors, the children were informed that if they opened the door of the seclusion room they would receive a 24-hour unit restriction. Four months after the locking mechanisms were removed, a center-wide reward-and-privilege behavioral level system was instituted successively on each of the three units. This behavioral level system was implemented over a 2-month period from April 27 to June 22, 1987, beginning with the unit for older, emotionally disturbed children, followed by the admission unit on May 25, 1987, and the unit for younger children with conduct disorders on June 22, 1987. Before the implementation of the center-wide reward-and-privilege behavioral level system, individual behavior programs had been implemented and group expectations for activities for daily living skills established on each of the individual units; however, a uniform system with criteria for specific rewards and privileges was lacking.

Three equal periods of time were examined for each of the three units (table 1). These time periods consisted of period 1—locked seclusion, period 2—unlocked seclusion, and period 3—unlocked seclusion

with a behavioral level system. Because the behavioral level system was implemented successively for each of the three units, the actual duration of each period varied from one unit to the next. Records of the number of seclusions, duration of each seclusion, staff-patient ratio, and number of sedative medications administered as needed had been kept regularly in all three units during the periods of this study. The daily mean number of patients in each unit for each period is given in table 1.

Throughout the study periods the clinical indications for the use of the seclusion room remained the same. Seclusion was used as a therapeutic treatment modality to protect the patient or others from physical injury, to decrease the level of stimulation when a child was in a state of agitation, and only when less restrictive measures and techniques had proven ineffective. The sequence of events leading to the child being placed in seclusion also remained consistent; it began with redirection and encouragement for the child to use a less restrictive area such as a bedroom or time-out bench to gain self-control and led to progressively more confined areas if clinically indicated. Mechanical restraints were never used. Staff would physically hold a child if necessary to protect the child either from self-abuse or from injuring others.

Medications used as needed throughout the study included diphenhydramine, chlorpromazine, and haloperidol. Indications for the use of medications as needed (for aggression or agitation) remained consistent throughout the study. These medications were administered only when less restrictive measures (i.e., counseling, redirection, time-out) had proven ineffective. The decision as to the timing of the administration of these medications varied according to the degree of agitation and aggression of the individual child.

The admissions criteria, staff-patient ratios, nature of psychopathology, unit rules and routine, and length of stay did not change appreciably during the time for which the data were collected. Approximately one-third of the children on each unit accounted for most of the use of seclusion and medication administered as needed, and, as expected, the majority of these children had diagnoses of behavior disorders. The mean length of stay during the study period was 14–16 months. The administrative direction of the units did

TABLE 2. Number of Days With No Seclusion and Daily Number of Seclusions on Three Child Psychiatric Inpatient Units During Periods With Locked and Unlocked Seclusion

Measure and Unit	Period 1: Locked Seclusion				Period 2: Unlocked Seclusion				Period 3: Unlocked Seclusion and Unit Privilege Behavioral Level System				Significance		
	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD	F	df	p
Days with no seclusion															
Admission unit	3	3	—	—	8	7	—	—	25	22	—	—	—	—	—
Younger children with conduct disorders	37	26	—	—	12	8	—	—	54	38	—	—	—	—	—
Older, emotionally disturbed children	61	71	—	—	41	48	—	—	37	43	—	—	—	—	—
Daily number of seclusions															
Total[a]															
Admission unit	—	—	5.05	2.40	—	—	4.20	2.70	—	—	2.49	2.60	30.2	2, 339	<0.0001
Younger children with conduct disorders	—	—	1.61	1.60	—	—	3.56	2.70	—	—	1.51	1.90	43.8	2, 423	<0.0001
Older, emotionally disturbed children	—	—	0.37	0.70	—	—	1.15	1.40	—	—	1.18	1.50	11.5	2, 252	<0.0001
On days with at least one seclusion[b]															
Admission unit	—	—	5.19	2.30	—	—	4.52	2.50	—	—	3.19	2.50	17.4	2, 303	<0.0001
Younger children with conduct disorders	—	—	2.18	1.40	—	—	3.89	2.50	—	—	2.40	1.80	24.0	2, 320	<0.0001
Older, emotionally disturbed children	—	—	1.28	0.60	—	—	2.20	1.30	—	—	2.06	1.40	4.9	2, 117	0.009

[a]Pairwise comparisons showed the following significant differences at the 0.05 level, with the Bonferroni correction: admission unit, all pairs; unit for younger children, periods 1 and 2 and periods 2 and 3; and unit for older children, periods 1 and 2 and periods 1 and 3.

[b]Pairwise comparisons showed the following significant differences at the 0.05 level, with the Bonferroni correction: admission unit, periods 1 and 3 and periods 2 and 3; unit for younger children, periods 1 and 2 and periods 2 and 3; and unit for older children, periods 1 and 2 and periods 1 and 3.

not change during that time, and both psychopharmacology and psychosocial treatments were used similarly in the three units throughout.

Data Analyses

We examined the following variables for each of the three units over each of the three periods: 1) the daily number of seclusions, 2) the daily total duration of seclusions, 3) the daily staff-patient ratio, 4) the daily number of medications administered as needed, 5) the percentage of days with no seclusions, 6) the percentage of days with no medication administered as needed, 7) the number of seclusions on days when there was at least one seclusion, and 8) the number of medications administered as needed when there was at least one such administration.

We used analysis of variance (ANOVA) to examine the differences within a unit across the three periods. We did not combine the three units in our analysis; rather, we report on each unit separately and compare the results across units. We also examined differences among the three pairs of periods within a unit and report results that were significant at the 0.05 level

after taking into account the Bonferroni correction. In the tables referred to later, we report for each unit the period mean and standard deviation, the results of the F test, along with the degrees of freedom, and the results of the pairwise comparisons. Although we present the data on the percentage of days with no medication administered as needed and with no seclusion, we do not analyze that data by ANOVA.

We used analysis of covariance (ANCOVA) to study the relationship between the staff-patient ratio and the main outcome measures of medications administered as needed and seclusion. For each unit we used the period as the grouping variable and the staff-patient ratio as the covariate. Analyses were done with BMDP (7).

We also addressed several potential concerns about the data. The skewness of the outcome variables could render the ANOVAs inaccurate. However, an examination of the appropriate histograms and probability plots indicated that the degree of skewness was not great, and the sample sizes were large enough to support the use of the standard analyses. In addition, we used log-transformed data to reduce the skewness and found that the conclusions mirrored those based on the

TABLE 3. Number of Days With No p.r.n. Medication and Daily Number of p.r.n. Medication Doses on Three Child Psychiatric Inpatient Units During Periods of Locked and Unlocked Seclusion

Measure and Unit	Period 1: Locked Seclusion				Period 2: Unlocked Seclusion				Period 3: Unlocked Seclusion and Unit Privilege Behavioral Level System				Significance		
	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD	F	df	p
Days with no medication															
Admission unit	72	63	—	—	85	75	—	—	68	60	—	—	—	—	—
Younger children with conduct disorders	125	88	—	—	44	31	—	—	86	61	—	—	—	—	—
Older, emotionally disturbed children	81	94	—	—	74	86	—	—	65	76	—	—	—	—	—
Daily number of p.r.n. administrations of medication															
Total[a]															
Admission	—	—	0.42	0.60	—	—	0.44	0.90	—	—	0.90	1.60	7.2	2, 339	0.0009
Younger children with conduct disorders	—	—	0.13	0.40	—	—	1.07	1.00	—	—	0.66	1.10	42.2	2, 423	<0.0001
Older, emotionally disturbed children	—	—	0.07	0.30	—	—	0.14	0.40	—	—	0.28	0.60	6.6	2, 252	<0.002
On days with at least one administration of medication[b]															
Admission	—	—	1.14	0.40	—	—	1.72	0.80	—	—	2.24	1.80	9.0	2, 114	0.0002
Younger children with conduct disorders	—	—	1.06	0.20	—	—	1.55	0.80	—	—	1.68	1.10	3.2	2, 168	0.04
Older, emotionally disturbed children	—	—	1.20	0.50	—	—	1.00	0.00	—	—	1.19	0.50	0.9	2, 35	0.42

[a]Pairwise comparisons showed the following significant differences at the 0.05 level, with the Bonferroni correction: admission unit, periods 1 and 3 and periods 2 and 3; unit for younger children, all pairs; and unit for older children, periods 1 and 3.

[b]Pairwise comparisons showed the following significant differences at the 0.05 level, with the Bonferroni correction: admission unit, periods 1 and 2 and periods 1 and 3; unit for younger children, periods 1 and 2 and periods 1 and 3; and unit for older children, none.

original scales. We also examined the effects of a few potential outliers and found that their removal did not affect our conclusions.

RESULTS

The Three Units

The three units in the children's center behaved in different ways in regard to unlocked seclusion and the institution of the behavioral level system; therefore, they will be described separately.

Admission unit. In the admission unit the mean number of seclusions decreased progressively from period 1 to period 3 (table 2). The mean number of seclusions in period 3 was less than half of that in period 1. Correspondingly, the percentage of days with no seclusion increased eightfold from period 1 to period 3. The mean number of seclusions on the days when there were any seclusions decreased in a fashion parallel to the mean number of seclusions.

In contrast, the mean number of sedative medications administered as needed in the admission unit more than doubled from the first period to the last (table 3). There was no major change in the percentage of days with no such medication (which was about 70% throughout the three periods), but there was a nearly twofold increase in the mean number of such medications on the days with any such medications, from the first period to the last; the second period was not significantly different from the third. Therefore, on the days when medication was administered as needed, more such medication was given.

Unit for younger children with conduct disorders. In this unit the mean number of seclusions did not vary substantially between the first and the third periods, but it more than doubled in the middle period. The percentage of days with no seclusions did not vary substantially between the first and third periods but dropped in the middle period. The mean number of seclusions on the days with any seclusions showed little change between the first and the last periods but increased substantially in the middle period (table 2).

TABLE 4. Cross-Classification of Daily Seclusion and p.r.n. Medication on Three Child Psychiatric Inpatient Units During Periods With Locked and Unlocked Seclusion

| | Number of Days | | | | | |
| | Period 1: Locked Seclusion | | Period 2: Unlocked Seclusion | | Period 3: Unlocked Seclusion and Unit Privilege Behavioral Level System | |
Unit and Seclusion	No p.r.n. Medication	At Least One p.r.n. Dose	No p.r.n. Medication	At Least One p.r.n. Dose	No p.r.n. Medication	At Least One p.r.n. Dose
Admission unit						
No seclusion	3	0	8	0	21	4
At least one seclusion per day	69	42	77	29	47	42
Younger children with conduct disorders						
No seclusion	37	0	10	2	50	4
At least one seclusion per day	88	17	34	96	36	52
Older, emotionally disturbed children						
No seclusion	60	1	41	0	30	7
At least one seclusion per day	21	4	33	12	35	14

In the unit for younger children with conduct disorders, the mean number of medications given as needed increased more than fivefold between the first and the third periods, while the number in the middle period was substantially higher. The percentage of days with no such medication showed corresponding changes, and the mean number of these medications on the days with any such medication showed a substantial increase from the first to the third periods (about 50%) again suggesting that there was a clustering of these medications (table 3).

Unit for older children with emotional disorders. In this unit the mean number of seclusions increased from the first period to the last two periods by a factor of three, while the percentage of days with no seclusions decreased correspondingly. The mean number of seclusions on days with any seclusions nearly doubled, suggesting a clustering of seclusions.

In this unit the mean number of medications administered as needed increased from the first to the last period in a progressive fashion by a factor of four, although the baseline level was low. The percentage of days with no such medication decreased somewhat from period 1 to period 3. The mean number of such medications on the days with any such medication did not show any change.

Medication Administered as Needed and Seclusions

We examined the relationship between medication administered as needed and seclusions within each period with daily data, although we should note that we regard this analysis as largely exploratory, since more detailed information than was available about the temporal proximity of each such medication and each seclusion within the day would be necessary to fully investigate this issue. Nevertheless, we first cross-clas-

sified each day according to whether or not any seclusion occurred and whether or not any medication was administered as needed (table 4). In the admission unit and the unit for younger children with conduct disorders, there was greater concordance between the two during periods 2 and 3 than in the baseline period. However, in the unit for older, emotionally disturbed children this trend was actually reversed. We also computed Pearson correlations between the medications and seclusions for days when both occurred. These correlations also pointed to the same conclusions. The correlation between periods 1, 2, and 3 and the units were as follows: admission unit, 0.1, 0.3, and 0.6; unit for younger children, −0.1, 0.5, and 0.5; and unit for older children, −0.3 for period 1, 0.5 for period 3, and for period 2, every day with a seclusion had exactly one seclusion. It should be noted that the sample sizes for both analyses for the unit for older children were quite small, placing some doubt on the solidity of the divergent results for that unit, where the use of seclusion was low throughout.

Staff-Patient Ratio

A possible explanation for the period changes could be that the staff-patient ratio changed from one period to the other in particular units. The daily staff-patient ratio was calculated as the number of patients present each day divided by the combined number of staff on the day and afternoon shifts. It is apparent that there was very little variation in the staff-patient ratio across the three periods within each unit, even though in two of the units there were statistically significant differences (table 5). Nevertheless, in order to see if the staff-patient ratio had an effect upon the number of medications administered as needed or seclusions, we used ANCOVA. For each unit we used the period as the

TABLE 5. Daily Staff-Patient Ratio on Three Child Psychiatric Inpatient Units During Periods With Locked and Unlocked Seclusion

| Unit[a] | Staff-Patient Ratio | | | | | | Significance | | |
| | Period 1:
Locked Seclusion | | Period 2:
Unlocked Seclusion | | Period 3: Unlocked
Seclusion and Unit
Privilege Behavioral
Level System | | | | |
	Mean	SD	Mean	SD	Mean	SD	F	df	p
Admission unit	1.78	0.30	1.75	0.30	1.72	0.40	1.0	2, 339	0.39
Younger children with conduct dis- orders	1.85	0.30	1.68	0.30	1.56	0.30	32.7	2, 423	<0.0001
Older, emotionally disturbed children	2.03	0.30	1.97	0.30	2.17	0.30	9.7	2, 252	<0.0001

[a]Pairwise comparisons showed the following significant differences at the 0.05 level, with the Bonferroni correction: admission unit, none; unit for younger children, periods 1 and 3 and periods 2 and 3; and unit for older children, all pairs.

grouping variable and the staff-patient ratio as the co-variate. We used a variety of outcome measures such as the daily number of medications administered as needed or of seclusions or the total daily duration of seclusions. In short, we found that while the period effect was typically highly significant, as reported earlier, the staff-patient ratio never had a significant coefficient.

Duration of Seclusions

The total daily duration (in minutes) of seclusion for all children in a unit was also analyzed with the F test (as before, for all days and for days in which there was at least one seclusion). The substantive conclusions from this analysis were, by and large, the same as those derived from the daily number of seclusions, so we omit a detailed discussion here. Since the durations were highly skewed, we also did the ANOVA after a natural log transformation; once again, this analysis yielded similar conclusions.

Lack of Contagion Across Units

Because of the geographical proximity of the units, we examined correlations among the three units on the common days available in the same period (86 days for each period). These correlations were close to zero in every case.

DISCUSSION

This retrospective study examined the clinical effects of the implementation of the Pennsylvania unlocked seclusion policy in three state hospital inpatient units housing children under 14 years of age. Although the composition of the units differed in regard to patient age, diagnostic mixture, and gains achieved in treatment, all units had a statistically significant increase in medication administered as needed from the baseline once the unlocked seclusion policy was implemented. Of particular clinical concern was the finding that after

the policy was implemented, on days when at least one such medication was administered, the mean number of such medications per day nearly doubled in the admission unit and the unit for younger children with conduct disorders. In short, during unlocked seclusion the younger, more disturbed children received more medication administered as needed, and there was increased clustering in the daily administration of this medication. Consequently, the targeted children, who were primarily one-third of the population of each unit, were likely to receive a greater number of tranquilizing agents, thus subjecting them to external psychopharmacological restraint and the possibility of adverse side effects.

The temporal association between the policy implementation and the frequency of the use of seclusion varied in the three units. A sustained rise in the frequency of seclusion occurred in the unit for older, emotionally disturbed children (which had the lowest baseline) and was accompanied by increased clustering of use of seclusion on the same days. In the unit for younger children with conduct disorders, there was a marked rise in the number and clustering of seclusions upon unlocking seclusion; this increase dropped to baseline levels at the same time that the behavioral program was instituted. In contrast, in the admission unit the frequency and clustering of seclusions decreased progressively. These differences are difficult to interpret. It is possible that the staff of each unit handled the change quite differently. For instance, because unlocked seclusion requires a higher degree of staff attention and a lower degree of staff sense of control than locked seclusion, the tendency in some might have been to use it more often and more widely in some units, perhaps at a lower threshold for preventive purposes, while others simply discarded it as ineffective. This interpretation receives some support from the fact that the implementation of the unit behavioral programs, which give staff both the necessary means and a sense of control, was associated with a decrease in the frequency of seclusions in the admission unit and the unit for younger children, both high users of locked seclusion at baseline. On the other hand, what the ev-

idence clearly suggests is that everyone at all times took refuge in medication administered as needed, regardless of their high or low use of unlocked seclusion. Furthermore, the unit behavioral programs were not associated with any consistent pattern of change regarding use of medication administered as needed.

The pattern of increasing positive correlations between medication administered as needed and seclusions within each period in the two high users of locked seclusion suggests that after seclusion was unlocked, when there was an overt episode of misbehavior on the unit, either it tended to affect several children at the same time or the staff responded in a more diffuse fashion or at a lower threshold or both. The end result was that seclusion and medication as needed were used at the same time, or at least on the same days, with an increasing number of patients in the units, thus contributing to a unit "contagion effect," the spread of acting out behavior to other children, and this seriously compromised the stability of the ward milieu. As mentioned before, in order to see if the increasing concordance of seclusion and medication administered as needed was actually accounted for by their happening not just on the same day, but also at the same time, an analysis of hourly data within a day would be necessary; however, the data were not available.

In this retrospective study causality cannot be established, and this study was not designed to do so. Nevertheless, our findings provide some support for the hypothesis that the effect of unlocking seclusion was an increased use of tranquilizing medications administered as needed and an increased clustering of their use with several patients in the same day, especially in the more behaviorally disturbed children. Our results do not exclude the possibility that further improvements in behavioral programming and psychopharmacological praxis, not on an as needed basis, or an increased staff-patient ratio may have decreased the use of medication administered as needed. These issues need to be tested in prospective studies.

Our findings also provide some support for the professional perception that the judicious and appropriate use of locked seclusion in child psychiatric inpatients may be clinically sound. It is certainly preferable to the frequent use of tranquilizing medication or to the patient inflicting harm. Given the findings in this study, we recommend that a prospective controlled study on the use of locked and unlocked seclusion be undertaken, controlling for staff-patient ratio, accuracy of diagnoses, adequacy of psychopharmacological interventions, and optimal behavioral programming, so that the necessary uses of locked seclusion in child psychiatric inpatient units can be determined. Such determination should take into account the totality of the risk-benefit ratio for child inpatient treatment across several outcome measures attuned to the individual patient's characteristics, staff morale and effectiveness, overall unit structure and function, and individual patient outcomes. Until then, locked seclusion with proper safeguards and frequent observations should be considered a proper therapeutic intervention for severely disturbed youngsters.

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Childhood Antecedents of Antisocial Behavior: Parental Alcoholism and Physical Abusiveness

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Hierarchical logistic regression was used to assess the independent and interactive effects of paternal alcoholism and physical child abuse on antisocial behavior in young adult men. Men with alcoholic fathers (N=131) did not report or exhibit more antisocial behavior than comparison subjects (N=70). Men with physical abuse histories, however, reported more aggressive and antisocial behaviors during a clinical interview and were rated by a clinical interviewer as more likely to act out aggression. Arrest records did not distinguish the groups. There was no evidence that paternal alcoholism and childhood victimization interacted to increase the risk of antisocial behavior.

(Am J Psychiatry 1990; 147:1290–1293)

Among contemporary theoretical perspectives, two independent but potentially interactive factors are thought to foster the development of antisocial behavior: having an alcoholic parent (1) and being abused as a child (2). Empirical research on the children of alcoholics suggests that they exhibit higher rates of antisocial behavior than control subjects, as defined by arrest rates and involvement with the police or the courts (3). Similarly, research on the long-term consequences of childhood abuse and neglect indicates that former abuse victims exhibit higher rates of antisocial behavior than control subjects, as defined by arrest records (4). Unfortunately, however, most studies on the etiology of antisocial behavior have examined either parental alcoholism or childhood victimization alone, rather than assessing their interaction. In addition, methodological problems such as biased subject selection procedures, lack of control groups, varied operational definitions of child abuse and alcoholism, and absence of base rate information have made it

difficult, thus far, to disentangle the distinctive antecedents of antisocial behavior.

The absence of data on the combined effects of parental alcoholism and child abuse on antisocial activity may be due, in part, to investigator assumptions regarding the etiology of such behavior. There is a common belief that child abuse is usually associated with parental alcohol misuse (5, 6), despite the lack of empirical data supporting this connection (7). This perspective discourages evaluation of interactive effects, since child abuse is assumed to be a consequence of, and thus overlap substantially with, parental alcoholism.

The present study was undertaken to assess the unique and interactive contributions of paternal alcoholism and history of childhood victimization to antisocial behaviors among young adult men. The data examined were acquired as part of a prospective study of alcoholism being conducted in Denmark. Advantages of the current study are that the subjects were not selected from among clinical or forensic samples and that clinical interview data, as well as arrest records and information on alcoholism treatment, were available for analysis.

METHOD

Subjects

As described previously (8, 9), all subjects were selected from a perinatal birth cohort consisting of 9,006 consecutive births that occurred between 1959 and 1961 at the State University Hospital in Copenhagen. The admission and discharge diagnoses of the 18,012 biological parents of the subjects were screened through the Danish Psychiatric Register in Aarhus, Denmark, where all such data have been registered since 1916. In addition, biological fathers who had received treatment for or diagnoses of alcoholism through other Danish hospitals or clinics were identified on the basis of a screening of the Municipal Alcohol Treatment Clinic records.

A total of 250 sons of alcoholic fathers were identified by this process. When we excluded those who had died, emigrated, or been adopted, 215 of these

men were available as potential subjects. The male comparison subjects were selected from the same perinatal birth cohort such that they were each matched to two sons of alcoholics on the basis of age, father's socioeconomic class, and mother's age at time of birth. When we excluded those who had died, emigrated, or been adopted, 102 comparison subjects were available for study.

All potential subjects were initially contacted by mail and were invited to participate in a follow-up study of the perinatal project. The follow-up study entailed 2 full days of each subject's time and involved physical examinations, clinical psychiatric interviews, electrophysiological assessment, and neuropsychological evaluation. A total of 201 subjects completed the evaluation procedures used in this study; 131 were sons of alcoholic fathers, and 70 were comparison subjects. As described in detail elsewhere (8), the rate of attrition due to refusal to participate, illness, or other reasons was 39.1% (N=84) among the sons of alcoholics and 31.4% (N=32) among comparison subjects. The age and socioeconomic class of the sons of alcoholics and comparison subjects who did and did not participate in the study did not differ significantly.

Procedure

The data were acquired in 1979 and 1980, when the subjects were 18 to 21 years old. Data obtained in two separate clinical interviews and through a screening of the Danish National Police Register were evaluated in this study.

Designation of paternal alcoholism. Subjects whose fathers had received treatment for or diagnoses of alcoholism at a Danish hospital or clinic made up the group categorized as having paternal alcoholism. Comparison subjects did not have family histories of alcoholism or other psychiatric disorders, according to registry information examined in Denmark.

Designation of physical abuse. During a 1–3-hour structured interview, trained clinicians obtained information from all subjects regarding their families, siblings, life crises, school activities and education, military service, financial affairs, and hobbies. In this interview, all subjects were asked whether they had experienced any of 20 specific life crises and to indicate the three crises that affected them the most. The information elicited during this interview concerned traumatic life events and stressors, such as the death of a family member or close friend; physical and mental illness, including alcohol and drug addiction in the family; unemployment; serious housing problems; and critical financial problems.

One item in the life crisis portion of the interview concerned whether subjects had ever been "beaten" by a parent. The clinical interviewer explained that being beaten "didn't just mean a slap on the face," but, rather, referred to repeated episodes of violent physical attacks or a single violent attack that was so aggressive that it resulted in a fracture or other physical injury

that required hospital treatment. The 32 subjects who responded affirmatively to this question were categorized as former victims of physical abuse. Eight of these subjects ranked being beaten as one of the three most significant events in their lives, and seven reported having been placed under the care of child guardians.

Evaluation of antisocial behavior. In a second, 1–2-hour structured clinical interview, subjects were queried about aggressive and antisocial behavior. The four self-report items selected from this interview were whether subjects 1) verbally expressed disagreement with others (tapping willingness to use verbal, as opposed to physical, methods of negative expression), 2) had ever threatened to hurt someone, 3) had ever hit someone in a fight, and 4) had engaged in any illegal act for which they had not been caught. The fifth item selected from this interview was the clinician's subjective rating as to whether the subject was prone to acting out aggressive impulses.

Criminality assessment. A screening of the Danish National Police Register was conducted in 1981. All subjects who had been apprehended by the police for traffic offenses, crimes of theft or financial gain, or sexual and violent crimes were identified. The total number of such apprehensions were recorded for each subject. For the present analysis, subjects who had been arrested twice or more were designated as repeat offenders and were compared with those who had no arrests or only one.

Statistical analysis. Dependent variables that are dichotomous can be analyzed by least-squares regression (in which case it is equivalent to a two-group discriminant analysis) or by logistic regression. When the predictors in a regression equation satisfy normality assumptions, least-squares regression constitutes an appropriate analytic approach to the data, but when the predictor variables (i.e., paternal alcoholism, history of abuse) are dichotomous, thus rendering the normality assumptions untenable, logistic regression constitutes an alternative analytic strategy. In logistic regression, the dependent variable is the logit (i.e., the logarithm of the odds of the dependent variable), and it is examined as a linear function of the independent variable(s) by using maximum likelihood ratios.

Six hierarchical logistic regression analyses (10) were performed. The dichotomous dependent variables in each of these analyses were the five interview items and the arrest record data. In each, the dichotomous paternal alcoholism variable was entered first, followed by the dichotomous abuse history variable, followed by the interaction of paternal alcoholism and abuse history. In the last two steps, improvement chi-squares (10) were calculated, providing tests of the hypotheses that abuse history and the interaction between paternal alcoholism and abuse history each significantly improved prediction of the dependent variable beyond that of paternal alcoholism alone. This

TABLE 1. Hierarchical Logistic Regression Analysis Predicting Aggression and Criminal Behavior in Young Men With Alcoholic Fathers (N=131) and Comparison Subjects (N=70) on the Basis of Paternal Alcoholism and Physical Beatings During Childhood

| Variable | Frequency | | Step 1: Alcoholic Father | | | | | | Step 2: History of Beatings | | | | | Step 3: Interaction | |
| | | | No | | Yes | | | | No | | Yes | | | | |
	N	%	N	%	N	%	χ^2 (df=1)	p	N	%	N	%	χ^2 (df=1)[a]	p	χ^2 (df=1)[a]	p
Usually expresses verbal disagreement	168	84	55	79	113	86	1.91	n.s.	146	86	22	69	6.10	0.01	0.34	n.s.
Has threatened to hurt someone	98	49	31	44	67	51	0.86	n.s.	77	46	21	66	4.09	0.04	0.00	n.s.
Has hit someone in a fight	141	70	45	64	96	73	1.74	n.s.	114	67	27	84	3.68	0.06	4.50	0.03
Rated as acting out	100	50	33	47	67	51	0.29	n.s.	79	47	21	66	3.73	0.05	0.70	n.s.
Has engaged in multiple illegal acts																
Never caught	51	25	14	20	37	28	1.68	n.s.	38	22	13	41	3.89	0.05	0.90	n.s.
Arrested	45	22	16	24	29	22	0.02	n.s.	37	22	8	24	0.10	n.s.	1.15	n.s.

[a]Chi-square tests at steps 2 and 3 represent the statistical significance of any improvement in prediction as a result of that variable being entered into the equation.

procedure affords a liberal test of the effects of paternal alcoholism and a conservative test of abuse effects (11).

RESULTS

More sons of alcoholic fathers (N=24, 18%) than comparison subjects (N=8, 11%) reported that they had been physically beaten, but this difference was not statistically significant ($\chi^2=1.62$, df=1, n.s.). Findings related to antisocial behavior are shown in table 1. Presence of an alcoholic father did not significantly predict any of the six antisocial variables at step 1. However, when paternal alcoholism was controlled, self-reported history of being beaten by a parent as a child was predictive of five of the six antisocial variables. Subjects who reported physical abuse as children indicated that they were less likely to verbally express disagreement with another person but were more likely to have threatened to hurt someone and to have hit someone in a fight, and they more frequently reported having committed multiple illegal acts for which they had not been caught. In addition, the clinical interviewer rated more of these subjects as likely to act out aggressive impulses. Physically abused subjects did not, however, differ from nonabused ones in terms of multiple arrests.

The interaction term permits evaluation of the joint impact of abuse and paternal alcoholism when the main effects are controlled (table 1, step 3). The interaction was significant for only one of the six variables, that of having hit someone in a fight. Inspection of this interaction revealed that subjects who were abused but who did not have an alcoholic father were significantly more likely to have reported hitting someone (100%, N=8) than were subjects who were not abused and who did not have an alcoholic father (60%, N=37). In contrast, in cases in which the father was alcoholic,

abused and nonabused subjects did not differ on this variable (79%, N=19; 72%, N=77, respectively).

DISCUSSION

Although slightly more sons of alcoholic fathers reported a history of physical abuse than did comparison subjects, this difference was not statistically significant. Thus, the current data support the notion that paternal alcoholism and physical abusiveness toward children may represent relatively independent phenomena. Multivariate analyses indicated that men with alcoholic fathers did not report or exhibit more antisocial behavior than comparison subjects, whereas men who were former victims of physical abuse more frequently reported such behaviors, were less likely to use verbal expression of disagreement, and were more often rated as likely to act out aggressive impulses. Finally, no evidence was obtained that antisocial behavior was more likely among men with histories of physical abuse and alcoholic fathers than among men with histories of physical abuse alone.

Because the subjects of this study have not yet passed through the entire risk period for committing criminal offenses, these results must be considered preliminary. In addition, the findings of this study are limited by the possibility that attrition in the subject sample could have mediated some of the between-group differences observed due to factors that remain unassessed. Similarly, no explicit methods for assessing the reliability of the items were included in this study, although the reliability of structured interviews administered by trained clinicians is usually moderate to high. In spite of these limitations, the preliminary findings of this study are striking when considered in the context of the research literatures on alcoholism and child abuse.

The results of this study are, to some extent, at variance with recent theoretical conceptualizations of al-

coholism (12). Most contemporary perspectives (12) and empirical evidence (13, 14) indicate that many individuals who receive diagnoses of alcohol abuse or alcoholism also manifest antisocial behavior. Since adult children of alcoholics constitute a group at high risk for developing alcoholism themselves (8, 9), one might expect that sons of alcoholics in the present study would have displayed or reported more aggressive or antisocial behavior. In addition, at least some studies indicate that children of alcoholic parents are more prone to aggressive acting out (3), theoretically by virtue of dysfunctional family dynamics thought to engender anger and other negative affects (15). The absence of such findings in the current study suggests either that parental alcoholism produces less trauma or psychological disturbance in children than previously thought, perhaps especially in nonclinical/nonforensic groups, or that aspects of the current study (e.g., sample size, subject's culture, age at assessment) preclude definitive conclusions in this area.

The results of the current study are, however, quite consistent with a growing body of empirical literature on the immediate and long-term effects of childhood physical abuse. In addition to literature indicating that former abuse victims may eventually become abusive parents themselves (16), studies of the long-term effects of physical maltreatment suggest that adults who were abused as children have a greater tendency to commit criminal acts (2, 4), as well as to display more psychological symptoms (17). In addition to supporting these findings, the present data indicate that it is not only the presence of aggressive behavior that discriminates abused subjects, but also the relative absence of verbal expressions of disagreement, which suggests that such individuals may characteristically choose physical over verbal methods of conflict resolution.

Given that the current data were collected in a relatively disparate culture and were derived from a methodology not specifically designed to evaluate the effects of physical child abuse, the findings relating child maltreatment and subsequent antisocial behavior are all the more significant. They suggest, for example, that child abuse may have psychological impacts that,

to some extent, are independent of cultural context and may thus lead to predictable effects in widely different settings. Further tests of this hypothesis require study of the antisocial and aggressive sequelae of physical abuse in other non-North American cultures. The current findings support the appropriateness of such an undertaking.

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CSF γ-Aminobutyric Acid in Alcoholics and Control Subjects

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*Alcohol has widespread effects on the γ-aminobu-
tyric acid (GABA) system in the brain. This system in
the brain is also postulated to have a role in anxiety,
and alcoholics have been reported to have more anx-
iety disorders. Therefore, the authors undertook a
study to compare CSF levels of GABA in abstinent
alcoholic patients and normal control subjects. There
was no significant difference between groups in CSF
levels of GABA. Also, there was no significant differ-
ence in GABA level between alcoholic patients with
histories of withdrawal seizures and those without
such a history.*
(Am J Psychiatry 1990; 147:1294–1296)

G amma-aminobutyric acid (GABA) is an inhibi-
tory neurotransmitter in the nervous system and
is widely distributed in the brain (1). Alcohol has both
presynaptic and postsynaptic effects on the central
GABA-ergic system that are presumed to result from
nonspecific effects of alcohol on cell membranes (2, 3).
Furthermore, alcohol has modulatory effects on bind-
ing sites at the GABA-benzodiazepine-chloride iono-
phore receptor complex, which contains a receptor for
GABA (4–7). Alcohol has also been shown to stimu-
late GABA receptor-mediated chloride transport in
this complex (8, 9).

This is of interest because benzodiazepines, used in
alcohol withdrawal, exert their effect by binding to a
receptor site in this complex, thereby increasing the
affinity of GABA for the $GABA_A$ receptor (10). Thus,
benzodiazepines increase the likelihood that GABA
will be effective in increasing chloride ion flux through
the channel by means of a functional coupling of the
two receptor sites (11, 12). Of further interest is a
report that a benzodiazepine antagonist prevents eth-
anol-induced intoxication in rats (13). Also, alter-
ations of the central GABA system have been impli-
cated in the pathophysiology of anxiety and depressive

disorders (14), of which there is a greater incidence
among alcoholics (15, 16).

There have been only two previous studies of CSF lev-
els of GABA among alcoholic patients. Both used a non-
specific radioreceptor assay measuring GABA-like activ-
ity. Hawley et al. (17) found no significant difference
between CSF levels of GABA-like activity ascertained
first when 12 alcoholics were in acute alcohol with-
drawal and then when they had recovered, an average of
10 days later. Goldman et al. (18) reported that alcohol-
ics without seizures had significantly higher CSF levels of
GABA-like activity than either alcoholics with seizures or
neurological control subjects.

We decided to test the hypothesis that there would
be a significant difference between alcoholic patients
and control subjects in CSF levels of GABA. We used
a specific ion-exchange chromatographic method to de-
termine CSF levels of GABA itself rather than GABA-
like activity.

METHOD

A consecutive series of 53 chronic alcoholic patients
(45 men and eight women) admitted to a clinical re-
search unit at the National Institutes of Health (NIH)
was studied. Their mean±SD age was 40.1±11.1
years. All of the patients met the *DSM-III* criteria for
alcohol dependence and the Research Diagnostic Cri-
teria (RDC) (19) for alcoholism. None had a major
medical disorder, a history of severe head trauma, or
neurologic disease. The alcoholics had not ingested al-
cohol for at least 3 weeks before the sampling of lum-
bar CSF.

The alcoholics were compared on CSF levels of
GABA with 22 normal control subjects (15 men and
seven women) who were recruited through the normal
volunteer office at NIH. Their mean±SD age was
41.0±20.1 years. The CSF GABA data of 13 of these
control subjects (all male) have been previously re-
ported (20). The control subjects were interviewed by
a research psychiatrist to exclude past or current psy-
chiatric disorder. They had normal findings on physi-
cal examination, including chest X-ray, ECG, and rou-
tine blood tests, and had been medication free for at
least 2 weeks before the study. All of the patients and
control subjects followed a low-monoamine, alcohol-
free, and caffeine-restricted diet during the study.

The alcoholics and control subjects underwent lumbar puncture at 9:00 a.m. after having fasted since midnight and having remained resting in bed in the morning for at least 2 hours following brief bathroom privileges. The subjects were placed in the left lateral decubitus position, and 32 ml of CSF were obtained. The first 12 ml of CSF were collected as a pool, mixed, placed on ice at the bedside, and subsequently divided into aliquots. A further 20 ml of CSF were collected into separate 1-cc tubes. All aliquots were kept frozen at −80 °C until assay. In the week of the lumbar puncture, the Hamilton Rating Scale for Depression (21) was completed for all of the alcoholics; items 10 (psychic anxiety) and 11 (somatic anxiety) were summed to yield an anxiety subscore.

CSF levels of GABA were determined in duplicate by ion-exchange chromatography coupled with fluorometric detection (22, 23). Duplicate analyses consistently exhibited variation of 5% or less. The same aliquots of CSF (the 26th ml) from the alcoholics and the control subjects were used. CSF levels of monoamine metabolites were measured by using high-pressure liquid chromatography with electrochemical detection (24). These CSF monoamine data are examined here only for correlations with CSF levels of GABA.

Because for the total group of subjects and for the alcoholics there was a significant negative correlation between CSF levels of GABA and age (r=−0.31, N=75, p<0.007, and r=−0.33, N=53, p<0.02, respectively), we used analysis of covariance with age as a covariate in the statistical analysis. Pearson's method of correlation was also used, and an analysis of statistical power was performed (25).

RESULTS

There was no significant difference between the 53 alcoholics and the 22 control subjects in CSF levels of GABA (mean±SD=94.7±42.1 and 107.7±51.8 pmol/ml, respectively; F=1.60, df=1, 72) (figure 1). The male and female alcoholics had similar CSF levels of GABA (94.9±41.9 and 93.9±46.3 pmol/ml, respectively). The male control subjects had nonsignificantly lower CSF levels of GABA than the female control subjects (102.0±42.3 and 120.0±70.3 pmol/ml, respectively; t=0.75, df=20). Two-way analysis of variance showed no significant difference for group (F=1.01, df=1, 74) or sex (F=0.26, df=1, 74) and no significant Group by Sex interaction (F=0.49, df=1, 74). There was no significant difference in CSF levels of GABA between alcoholics who did (N=7) and those who did not (N=35) have histories of withdrawal seizures (96.3±32.3 and 93.8±42.7 pmol/ml, respectively; F=0.2, df=1, 40).

Among the control subjects there was a significant negative correlation between CSF levels of GABA and CSF levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) (r=−0.45, N=22, p<0.04). Among the alcoholics this correlation was not significant (r=−0.09,

FIGURE 1. CSF Levels of GABA In Alcoholics and Control Subjects[a]
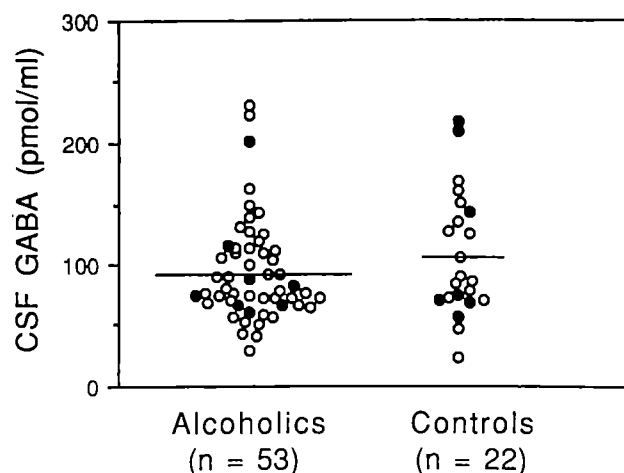
[a]Horizontal lines indicate means. Female subjects are indicated by black circles. There was no significant difference between the two groups of subjects.

N=48). There were no significant correlations among the male alcoholics between CSF levels of GABA and either the total Hamilton depression score or the anxiety subscore (r=0.08, N=23, and r=0.10, N=23, respectively).

DISCUSSION

In this study there was no significant difference in CSF levels of GABA between a large group of alcoholics and normal control subjects. However, the power analysis showed that with our sample size, a power of 0.20 was achieved, suggesting that a larger sample would be needed to draw more than preliminary conclusions from our study.

There was a significant negative correlation between CSF levels of GABA and age in both the total group of subjects and the group of alcoholic patients. A negative correlation with age has also been reported in other CSF studies of GABA (23, 26–28). We adjusted for this negative age effect by analyzing all the CSF GABA data with age as a covariate.

All of these alcoholic and control subjects were studied as inpatients in the same way, on the same clinical research unit, and over the same period of time, and all were receiving a low-monoamine diet. Also, the same aliquots of CSF from both the alcoholics and the control subjects were used for the quantification of CSF levels of GABA. The storage times of the CSF samples were similar for both groups (approximately 2 years). The CSF samples were not thawed before assay. Thus, many of the potential methodological problems of studies of CSF levels of GABA (24) were minimized and are unlikely to account for the lack of significant differences we found in the study.

GABA-ergic neurotransmission is thought to have a

role in anxiety and depressive disorders as well as in epilepsy. In this study there was no significant correlation between CSF levels of GABA and either the total Hamilton depression score or the anxiety subscore. Future studies should use anxiety rating scales more specifically designed for recording anxiety symptoms. Also, there was no significant difference in CSF levels of GABA between alcoholics with and without histories of withdrawal seizures. However, a larger group of subjects is needed to definitively address this issue.

Among the 22 control subjects, there was a significant negative correlation between CSF levels of GABA and CSF levels of the norepinephrine metabolite MHPG, which we had observed earlier among 13 of these control subjects (20). This is interesting because preclinical studies have suggested that GABA may inhibit central norepinephrine release (28).

In summary, the results of this study suggest that central GABA-ergic systems may not show marked abnormality among alcoholics studied a few weeks after alcohol withdrawal. However, studies of CSF GABA among alcoholics both when they are drinking and when they are in acute alcohol withdrawal are yet to be conducted.

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Cognitive Effects of Corticosteroids

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*In three independent studies with different designs
and groups of subjects, the authors found that 1) de-
pressed patients who did not suppress cortisol when
given dexamethasone (compared to suppressors and
normal control subjects), 2) healthy volunteers given a
single 1-mg dose of dexamethasone (compared to
those given placebo), and 3) healthy volunteers given
80 mg/day of prednisone for 5 days (compared to
those given placebo) all made significantly more errors
of commission in verbal memory tasks, with no sig-
nificant change in their rates of errors of omission.
These findings raise the possibility of specific cortico-
steroid-related cognitive impairments.*
(Am J Psychiatry 1990; 147:1297–1303)

E xcessive circulating levels of endogenous and ex-
ogenous corticosteroids are frequently associated
with cognitive impairment (1, 2). For example, pa-
tients with Cushing's syndrome and medically ill
patients treated with exogenous corticosteroids fre-
quently develop difficulties with attention, concentra-
tion, and memory (3–9). Starkman and Schteingart (3)
conducted semistructured interviews with 35 patients
with Cushing's syndrome and found that 66% had
difficulty in concentration and 83% had memory dif-
ficulties. The severity of the patients' overall impair-
ment was directly correlated with their levels of corti-
sol and ACTH and lessened in proportion to the
therapeutic lowering of their plasma cortisol levels (4).
Whelan et al. (5) also tested 35 patients with Cushing's
syndrome with the Michigan Neuropsychological Test
Battery and found that 22 of these patients had at least

mild cognitive impairment. Varney et al. (6) reported
six cases in which patients receiving high doses of cor-
ticosteroids for a variety of medical illnesses (which
largely did not affect the CNS) developed reversible
dementia-like syndromes. The symptoms, which in-
cluded decreased attention, concentration, retention,
and mental speed, were not related to concurrent ste-
roid psychosis or delirium. Hall et al. (7) noted a 57%
incidence of intermittent memory impairment in the
group of corticosteroid-treated medically ill patients
they studied.

Patients with depression have also been noted to
exhibit a variety of deficits in cognitive functioning,
including decrements in simple and complex atten-
tional tasks, verbal and visual memory, encoding, stor-
age, and retrieval (10–12). Several studies have sug-
gested that depressed patients with hypercortisolemia
or hypercortisoluria and those who fail to normally
suppress cortisol in response to dexamethasone show
particularly pronounced cognitive deficits. For exam-
ple, Rubinow et al. (13) observed a significant relation-
ship between mean urinary free cortisol levels in de-
pressed patients and the number of errors they made
on the Halstead Category Test, although such a rela-
tionship was not observed in normal control subjects.
Further, several (14–19) but not all (20) studies have
reported that depressed patients who do not suppress
cortisol when given dexamethasone demonstrate great-
er cognitive deficits than do depressed patients who
suppress normally.

Prior studies of the relation between corticosteroids
and cognitive performance have been hampered by the
lack of prospective designs and by the use of subjects
with active medical or psychiatric illnesses. Naturalis-
tic studies of the relation of hypercortisolemia, non-
suppression of cortisol in response to dexamethasone,
and high circulating levels of medically prescribed cor-
ticosteroids to cognitive performance have generally
been unable to separate cognitive effects related to the
corticosteroids themselves from those secondary to the
underlying illnesses. The most direct way to assess the
effects of corticosteroids on cognition is to administer
them prospectively to currently healthy subjects, as
was done in studies 2 and 3 reported in this article.
Prior studies of the relation of corticosteroids to cog-
nitive performance have also generally failed to docu-
ment the specific ways in which cognition is altered.

Along with a growing awareness of the complexity of human cognition (21–24), some studies have suggested that memory may be altered by drugs or disease states in very specific ways (25–27). Analysis of such specific changes may yield important clues to the psychobiology of cognitive function as well as the specific mechanisms of drug action (21). We recently completed three independent studies of the relation of corticosteroids to cognitive function and performed differentiated analyses of the associated cognitive impairments in each. Despite the differing methods and designs of these three studies, we present the results together in order to identify a spectrum of corticosteroid-associated cognitive changes and to highlight the common findings that emerged.

METHOD

Study 1

Twenty-one depressed patients (nine who were non-suppressors of cortisol and 12 who were suppressors when given the dexamethasone suppression test [DST]) and 12 normal volunteers were tested. All subjects gave informed consent to participate in the study. Nonsuppression was defined as a cortisol value of >5.0 µg/dl at 8:00 a.m., 4:00 p.m., or 11:00 p.m. on the day following a midnight oral dose of 1 mg of dexamethasone. Baseline serum cortisol levels were also determined at 4:00 p.m. on the day before dexamethasone administration. All patients satisfied the *DSM-III* criteria for major depression and had scores of at least 17 on the Hamilton Rating Scale for Depression (28). Nonsuppressors and suppressors did not differ significantly on depression ratings (nonsuppressors, mean±SD=20.0±4.47; suppressors, 19.08± 3.48; t=0.52, df=19, n.s.). All of the patients had been medication free for at least 1 week at the time of the study. The three groups did not differ significantly in age, years of education, or scores on the vocabulary subtest of the WAIS. Memory testing was done within 1 week of the DST (but not less than 36 hours following it), always in the afternoon. Memory was tested with a recognition task adapted from Wallach et al. (29). In this task the subjects listened to a taped recording of a 16-word list presented at the rate of one word every 10 seconds. The subject was instructed to repeat each of the 16 words and to think of what the words meant to him or her. Following presentation of the list, the subject was involved in a 15-minute motor distraction task. The subject then listened to a 50-word list containing the 16 original target words and 34 background distractor words and was asked to discern between targets and distractors. Target and distractor items were matched for frequency of written use and degree of imagery. The subjects received practice on the memory task before being tested.

Study 2

Forty-nine medication-free and caffeine-free normal subjects were recruited from the Normal Volunteer Office of the National Institute of Mental Health (NIMH) and screened for absence of personal or family history of psychiatric illness with the Schedule for Affective Disorders and Schizophrenia (SADS) (30). Thirty of the subjects were given dexamethasone and 19 were given placebo; the two groups were matched for age and education. All of the subjects gave informed written consent to participate in the study but were blind to its rationale. All had been free of any medication for at least 3 weeks before beginning the study. Memory testing was done at 4:00 p.m. 1 week before the administration of dexamethasone (1 mg p.o.) or placebo at 11:00 p.m. and on the day after. In this memory test, which we had used previously (10, 26), the subjects were read a list of 12 semantically related words (e.g., types of furniture) at a rate of one word every 3 seconds. Six of these words were read once and six were read twice in random order (for a total of 18 presented words). As a test of attention, subjects were asked to signal whenever they heard a repeated word. Following a 90-second verbal distractor task, subjects were asked to freely recall the previously presented words. Immediately following that, subjects were presented a list of 24 words containing the original 12 target words and 12 distractor words (i.e., words not previously presented) from the same semantic category and were asked to identify the previously presented target words. Lists of words from different semantic categories were presented on the 2 test days to minimize interlist interference effects. The volunteers received practice on the memory task before being tested.

Study 3

Eleven medically healthy, medication-free and caffeine-free volunteers were recruited from the NIMH Normal Volunteer Office and screened for personal psychiatric history with the SADS. All gave written informed consent to participate in the study. Four of the volunteers had histories of adjustment disorder (N=3) or alcohol intoxication (N=1); the remaining seven volunteers had no psychiatric history. All of the volunteers were psychiatrically healthy and free of alcohol or substance abuse at the time of the study and had been so for at least 2 years. They were given prednisone (80 mg p.o. daily for 5 days) in a double-blind manner (31). Memory testing was done once during an initial 5-day placebo period, once after 4 days of prednisone administration, and once again 7 days after discontinuation of the prednisone (during a postdrug placebo period). The memory test we used was similar to that described in study 2, except that the free recall and recognition tasks were performed 24 hours after list presentation. No medications were changed between learning and recall/recognition. As in study 2, lists of

words from different semantic categories were presented on the 3 test days to minimize interlist interference effects, and the volunteers received practice on the memory task before being tested.

Analysis

Data in study 1 were analyzed by one-way analysis of variance (ANOVA) (group). Data in study 2 were analyzed by two-way ANOVA with repeated measures (Group by Time). Data in study 3 were analyzed by one-way ANOVA with repeated measures (time). In addition, we carried out a signal detection analysis on the recognition test data. In this analysis the rate of "hits" (old, previously presented items classified as old) and "false alarms" (new, never-presented items classified as old) were jointly analyzed to determine d', a measure of the subject's ability to discriminate between old and new items, and β, a measure of the subject's response bias (or criterion for accepting items as old) (32). The d' is estimated as the z score of the false alarm rate minus the z score of the hit rate ($d' = z_{FA} - z_H$); higher d' values indicate greater discriminability. The β is estimated as the ratio of the ordinate of the signal (old) distribution at the criterion to the ordinate of the noise (new) distribution at that criterion ($\beta = F_s(c)/F_n(c)$). Neutral response biases yield $\beta = 1$, whereas liberal response biases yield $\beta < 1$ and conservative response biases yield $\beta > 1$. For hit rates that equaled 1.0 or false alarm rates that equaled 0 (for which signal detection measures are undefined), a mathematical correction described by Snodgrass and Corwin (32) was applied.

RESULTS

Study 1

There was no significant difference between depressed cortisol suppressors, depressed nonsuppressors, and normal control subjects on total correct responses (correctly identifying target words) in the recognition test (figure 1, top). However, depressed nonsuppressors showed a much higher rate of errors of commission (incorrectly identifying distractors as targets) than did the depressed suppressors and the normal control subjects (F=11.50, df=2, 30, p<0.0002) (figure 1, bottom). Signal detection analysis revealed a trend toward a significantly lower d' for the nonsuppressors than for the suppressors (mean±SD=1.92± 0.84 and 2.67±0.86, respectively; t=1.93, df=19, p< 0.07) but no difference in response bias (β) (2.02±3.51 and 3.05±3.38, respectively; t=0.66, df=19, n.s.). The depressed patients' baseline 4:00 p.m. cortisol levels tended to be directly correlated with numbers of commission errors ($r_s=0.38$, N=21, p<0.10) but not omission errors.

FIGURE 1. Mean Numbers of Target Words Correctly Recognized (top) and Distractor Words Incorrectly Identified as Targets (Commission Errors) (bottom) in Study 1 by Depressed Patients (Cortisol Suppressors and Nonsuppressors) and Control Subjects
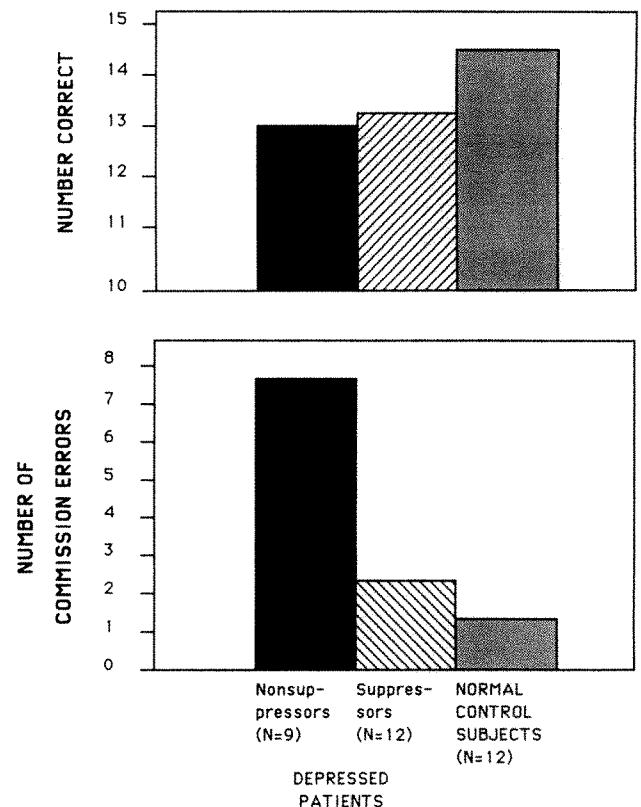
Study 2

Dexamethasone was associated with a significantly higher rate of errors of commission, or intrusions (i.e., self-generated words) into free recall, than was placebo (table 1). There were no significant differences between the dexamethasone and placebo groups on measures of attention, correct free recall, and total correct recognition. There was a nonsignificant increase in incorrect identification of distractors as targets in the recognition task after dexamethasone (table 1). Signal detection analysis revealed no significant change in d' or β in the recognition task in either group (table 1).

Study 3

Prednisone was associated with a significantly higher rate of errors of commission (i.e., incorrectly identifying distractors as target words) than was placebo during the test of recognition memory (table 2). This specific impairment returned to normal 7 days after discontinuation of the prednisone. There were no significant effects of prednisone on measures of attention, free recall, and correct recognition of target words (table 2). Signal detection analysis revealed a highly significant decrease in d' during prednisone

TABLE 1. Effect of a 1-mg Dose of Dexamethasone or Placebo on Memory Performance of 49 Healthy Volunteer Subjects in Study 2

Group/Time of Test	Attention		Free Recall		Intrusions		Number of Words				d'^a		β^b	
							Correct Recognition							
							Targets		Distractors					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Dexamethasone (N=30)														
Before	5.63	0.67	8.33	2.09	0.70	0.99	11.13	1.11	9.23	2.51	2.31	0.89	0.76	0.58
After	5.63	0.56	7.80	1.80	1.36^c	1.83	11.30	0.84	8.63	2.61	2.20	0.79	0.66	0.57
Placebo (N=19)														
Before	5.42	0.77	8.47	1.71	0.89	1.49	11.70	0.56	9.95	1.90	2.72	0.59	0.59	0.40
After	5.42	0.90	8.16	1.71	0.53	0.77	11.40	0.61	9.74	2.28	2.56	0.81	0.73	0.39

^{a}Measure of subject's ability to discriminate between previously presented and never-presented items.
^{b}Measure of subject's response bias.
^{c}Significant Group by Time interaction (F=3.80, df=1, 47, p=0.05).

TABLE 2. Effect of Prednisone (80 mg/day for 5 days) on Memory Performance of 11 Healthy Volunteer Subjects in Study 3

Time of Test	Attention		Free Recall		Intrusions		Number of Words				d'^a		β^b	
							Correct Recognition							
							Targets		Distractors					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	5.64	0.67	5.82	3.34	2.27	1.95	10.27	2.20	7.55	2.46	1.54	0.55	0.65	0.46
Day 4 of prednisone	5.27	0.90	4.55	2.46	2.45	2.21	9.45	2.21	5.91^c	2.81	0.89^d	0.86	0.77	0.38
7 days after prednisone	5.54	0.52	5.81	2.09	1.45	1.21	10.55	1.04	8.09	2.74	1.76	0.93	0.68	0.20

^{a}Measure of subject's ability to discriminate between previously presented and never-presented items.
^{b}Measure of subject's response bias.
^{c}Significant effect of time (F=4.28, df=1, 10, p<0.05).
^{d}Significant effect of time (F=6.97, df=1, 10, p=0.005).

treatment; post hoc tests revealed significant differences from both placebo periods (p<0.05). There was no significant change in β (F=0.64, df=1, 10, n.s.) (table 2).

DISCUSSION

Each of the three studies indicated a relationship between corticosteroids and cognition. In study 1 we found that patients who showed evidence of pituitary-adrenal disinhibition were more likely than those who did not to show evidence of cognitive dysfunction in the context of their depressive illness. This deficit can best be described as a relative inability to discriminate previously presented relevant information (targets) from irrelevant new information (distractors) in a test of recognition memory. In study 2, using a different design and testing additional aspects of cognitive function, we found that a single dose of dexamethasone induced an increase in the rate of intrusions into free recall in healthy volunteers. In study 3, using a similar design but with a longer time latency between learning and recall/recognition and a greater exposure of the subjects to the exogenous corticosteroid prednisone, we again found a relative inability to discriminate targets from distractors in recognition memory when the

subjects were taking the drug. Although one should not conclude that the relationships are identical in each of these different paradigms, the phenomenologic similarity of these findings is intriguing. In each of the three studies, increases in errors of commission were observed although there was no significant alteration in attention or errors of omission. The increased rates of errors of commission were not accounted for by changes in response bias ("yea saying"), since no significant changes in β were observed. Rather, weaker subject "sensitivity" and poorer discriminability of "signal" and "noise" distributions are suggested as possible explanations by the significant decrease in d' in the prednisone-treated volunteers and by the almost significant decrease on this measure in the depressed patients who did not suppress cortisol in response to dexamethasone. The lack of significant change in d' in the dexamethasone-treated volunteers may have been secondary to their relatively brief exposure to the exogenous corticosteroid and to the fact that their increased propensity to make commission errors was seen in the free recall rather than the recognition task. (Signal detection analysis is not feasible with free recall data.)

Cognitive impairment associated with hypercortisolemia or with nonsuppression on the DST has been previously described (13–19, 33); however, the speci-

ficity of the impairment that we observed is noteworthy. Our findings are consistent with the unpublished report of Deptula (34) that depressed nonsuppressors of cortisol show a greater rate of false alarms in verbal recognition tasks, with no difference in rate of omission errors, than do depressed cortisol suppressors and control subjects. Deptula also found that 4:00 p.m. postdexamethasone cortisol levels in depressed patients were significantly correlated with rates of false alarms, but not misses, in verbal memory. We have previously reported that cognition fails in specific ways in amnestic and dementing illnesses (25, 26) and in response to different drugs, such as benzodiazepines (27) and scopolamine (35). The present results suggest that corticosteroids induce yet another specific form of cognitive failure, further highlighting the psychobiologically differentiated nature of cognition. It should be noted that the specific deficit which we observed with corticosteroids is quite similar to the deficit sometimes noted in the context of normal aging (36, 37), as well as that seen with the administration of methamphetamine in normal subjects (38). In such studies, subjects appear to direct more attention to irrelevant stimuli, which results in decreased processing of relevant stimuli and poorer performance.

In order to interpret our data properly, several issues require explication. 1) Nonsuppression of cortisol in response to dexamethasone is not equivalent to basal hypercortisolemia (unpublished 1981 paper by G.N. Asnis et al.), although in depressed patients there is a substantial overlap between these conditions (39). Sikes et al. (17) observed that cognitive impairment was more closely associated with nonsuppression of cortisol in response to dexamethasone than with basal hypercortisolemia or hypercortisoluria in depressed patients, although measures of the latter were significantly correlated with cognitive impairment (18). They argued that CNS dysfunction, related to hypothalamic-pituitary-adrenal axis disinhibition, is more clearly related to the cognitive impairment than are elevated circulating corticosteroid levels per se. In our study of depressed patients, we also found that basal serum cortisol levels were only weakly associated with cognitive performance, perhaps because random basal cortisol measurements are typically variable. Our data on exogenous corticosteroids in healthy volunteers, however, suggest that such corticosteroids alter performance on specific cognitive tasks. 2) Although phenomenologically similar impairments were seen in our three studies, exogenous corticosteroids may have CNS effects that are very different from those of endogenous corticosteroids (40), and states of endogenous hypercortisolemia may also be associated with increased levels of ACTH and/or corticotropin-releasing hormone (41). Therefore, it is not appropriate to extrapolate uncritically from the effects of exogenous corticosteroids to those of endogenous ones. 3) Since different testing paradigms were used in the three studies, there may be some limitation on overall generalizations that can be drawn from them. 4) Whereas cog-

nitive deficits were clinically apparent in the patients in study 1, the deficits of the subjects in studies 2 and 3 were statistically, but not clinically, apparent (i.e., they were not grossly discernible). Only two of the 11 volunteers in study 3, for example, complained of confusion or difficulty concentrating while receiving prednisone. Longer-term treatment with corticosteroids has been associated with clinically significant cognitive impairment, however (6, 7, 9). 5) Corticosteroid associations with cognitive performance may be quite complex and may vary with both age and diagnosis of the subjects tested (13, 42). Therefore, our results should not be extrapolated to samples with different diagnoses and with different age ranges.

The mechanisms by which corticosteroids may alter cognition are unknown. However, our findings appear to be consistent with electrophysiological findings that acute administration of cortisol to human subjects reduces the average evoked potential response to relevant but not irrelevant stimuli (decreased signal-to-noise ratio) (43). Thus, cortisol may lead to less salient encoding of meaningful stimuli and may impair selective attention, thereby reducing an individual's ability to discriminate relevant and important information from irrelevant and unimportant information. Such an explanation would be consistent with our prior report that depressed patients who do not suppress cortisol in response to dexamethasone fail to dishabituate (show response specificity) to novel stimuli (44).

Changes in hippocampal activity may also be involved in steroid-related cognitive changes. Hippocampal lesions are most evident in tasks that maximize interference between present learning and similar prior learning and in tasks in which correct selection of a response from among several alternatives is required (45). McEwen (46) hypothesized that corticosteroids act to suppress the ability of the hippocampus to filter out behaviorally irrelevant stimuli, and corticosteroids have been shown to block the improvement in selective attention that follows dorsal noradrenergic bundle stimulation (47). Further, Sapolsky and McEwen (48) demonstrated that elevated levels of corticosteroids can decrease the number of corticosteroid-receptor-bearing hippocampal neurons. Such changes could conceivably lead to long-lasting cognitive or behavioral alterations (9). The theory of hippocampal involvement in the cognitive effects of corticosteroids is particularly cogent because the hippocampus contains the highest concentration of corticosteroid binding sites in the brain (40, 49). This relationship is likely to be complex, however, given the differential CNS binding patterns of endogenous and exogenous corticosteroids (40).

Finally, corticosteroid-related changes in memory may be related to increases in arousal. Although the term "arousal" is somewhat ambiguous, it does provide a useful link in relating neuroendocrine data to data derived from psychological investigations (2). One of the first attempts to relate arousal to cognitive performance was the Yerkes-Dodson law (50), which

stated that arousal has an inverted U-shaped relationship with cognitive efficiency. That is, peak efficiency is achieved at a moderate level of arousal, whereas either low or high levels of arousal are associated with a diminution in cognitive efficiency. Most theories of why arousal causes a change in cognitive performance have focused on changes in attentional abilities. Easterbrook (51), for example, postulated that increased arousal leads to a reduction in the range of cues used or admitted for attentional input ("attentional narrowing"). At an optimal level of arousal, there is good separation between noise (irrelevant) and signal (relevant) inputs. With states of overarousal, however, there is an overselectivity in input, so that there is decreased use of even relevant cues, which also leads to impaired performance. It is commonly appreciated, however, that increased arousal may lead to increased attending to irrelevant information and internal cues (52–57). These deviations from the original formulation by Easterbrook (51) may be accounted for by a modified theory (24). In addition to the attentional inputs of signals and externally generated noise, there may be a third source of attentional input, namely, internally generated noise (24). In this hypothetical model, as arousal is increased to a supraoptimal level, there is an increase in input of signals that are internally generated but irrelevant, which leads to an increased tendency toward internal distractibility, i.e., increased intrusion errors and errors of commission. While the connection between hypercortisolemia and arousal is ambiguous, this conceptual schema may prove heuristically useful.

CONCLUSIONS

Recognition of corticosteroid-related cognitive pathology may be clinically important, as such pathology may impair patients' abilities to process new information, to filter out distracting information, and to respond appropriately to environmental changes. Clarification of these effects should allow a better delineation of the cognitive symptoms that are related to patients' underlying illnesses and those which are related to their circulating corticosteroid levels. In a more speculative vein, hormonal treatments specifically aimed at diminishing cortisol activity (e.g., RU 486 [58], mitotane [4], and ketoconazole [59]) could prove clinically effective in ameliorating cognitive impairments associated with endogenous hypercortisolemia. Patients with Cushing's syndrome, for example, who are treated with such agents show improvements in attention, concentration, and memory (4, 58) and decreases in confusion (60) in parallel with treatment-induced decreases in urinary cortisol levels (4). We are currently exploring such treatment effects in hypercortisolemic patients with major depression.

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The Clinical Presentation of Command Hallucinations in a Forensic Population

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In a forensic population, patients with command hallucinations (N=25) were compared to two groups of psychotic patients: those with noncommand hallucinations (N=24) and those without hallucinations (N=16). The three groups did not differ in overall impairment as measured by the Global Assessment Scale and the Social Behavior Rating Schedule. However, the group with command hallucinations differed in the content of their hallucinations (more aggression, dependency, and self-punishment themes), and nearly one-half did not report or denied their command hallucinations to the assessment team. Many patients (N=11, 44%) reported that they frequently responded to hallucinatory commands with unquestioning obedience.

(Am J Psychiatry 1990; 147:1304–1307)

Retrospective studies of command hallucinations have emphasized the importance of such hallucinations to the treatment and management of psychotic patients. Research suggests that roughly one-third of hallucinating inpatients experience hallucinatory commands during their current episode (1, 2). Less is known about the frequency with which command hallucinations are obeyed or result in violent behavior (3). Estimates of the latter range from 0% (1) to 15% (4). Within a forensic context, Rogers (5) found that 5.8% of individuals evaluated for insanity had responded to command hallucinations in committing their criminal offenses; while this percentage appears modest, it represented nearly one-half (43.0%) of all forensically referred individuals with auditory hallucinations.

Dramatic case studies underscore the potentially devastating consequences of command hallucinations, which may result in self-mutilation (6, 7) and even death (3). Recent attempts to classify patients with hal-lucinatory commands have ranked them in the severely impaired range on both the Global Assessment Scale (GAS) (8) and its recent adaptation for *DSM-III-R*. However, Hellerstein and associates (2) found no significant differences in treatment (i.e., medication levels) or problematic behavior (i.e., assaultive or suicidal) between patients with and without command hallucinations, although their results are partially confounded by the clinical staff's active attempts to control these factors. Thus, the overall degree of influence that command hallucinations have on day-to-day functioning and whether this influence is primarily maladaptive (9) remain unanswered questions.

Our understanding of command hallucinations is limited both by the handful of studies from diverse settings and by the notable absence of standardized measures for evaluating the symptoms. The present study was designed to address the lack of standardized measures of symptoms, the characteristics of hallucinations, and general impairment. It also sought to establish differences in clinical presentation and impairment for patients with command hallucinations when compared to 1) patients with noncommand hallucinations and 2) psychotic patients without hallucinations. As an exploratory approach, nonpsychotic indicators of command hallucinations were investigated with a single-stage discriminant model. In addition, univariate comparisons were made for clinical characteristics and level of functioning.

METHOD

The study consisted of 65 psychotic inpatients who were recruited from an inpatient forensic assessment unit (Metropolitan Toronto Forensic Service, Clarke Institute of Psychiatry). Since all patients are referred by the metropolitan courts, the subjects were clinically heterogeneous and represented patients who typically exhibit problematic behavior (e.g., appeared mentally disordered at the time of arrest or were disruptive during the courtroom proceedings). The study group consisted primarily of men (92.3%, N=60); the mean± SD age was 32.41±8.34 years. Forty-four subjects (67.7%) were white, nine (13.8%) were black, three (4.6%) were Oriental, and five (7.7%) were East In-

TABLE 1. Rating of Verbal Content of Command and Noncommand Hallucinations[a]

Content	Command Hallucination Group (N=25)[b]		Noncommand Hallucination Group (N=24)[c]		Comparison	
	Mean	SD	Mean	SD	t[d]	p
Aggression	2.00	1.10	1.28	0.56	7.17	0.01
Companionship	2.08	1.10	2.95	0.92	8.12	0.007
Dependency	2.54	1.02	1.52	0.68	15.03	0.0004
Entertainment	1.96	0.86	2.67	1.15	5.54	0.02
Evaluation	2.25	1.02	2.24	1.04	0.00	n.s.
Indecision	3.08	0.93	2.33	1.11	6.09	0.02
Role identity	1.42	0.72	1.28	0.56	0.46	n.s.
Self-importance	3.09	1.12	2.75	1.02	1.05	n.s.
Self-punishment	2.21	1.22	1.43	0.68	6.79	0.01
Sexual identity	2.12	1.23	2.10	1.09	0.01	n.s.

[a]Content was rated on a 4-point scale based on Larkin's criteria (12).
[b]Experienced command hallucinations in the last 30 days.
[c]Experienced hallucinations in the last 30 days but no command hallucinations in the last 12 months.
[d]Two-tailed.

noncommand hallucinations (table 1). Command hallucinations had more aggressive and self-punishing content; patients with these hallucinations experienced helplessness and dependency on the auditory hallucinations and greater reliance on the hallucinations for advice and decisions than did patients with noncommand hallucinations. In contrast, patients with noncommand hallucinations experienced a more positive relationship with their hallucinations, seeing them as more friendly and entertaining than did those with command hallucinations. Clinicians may wish to reevaluate patients who deny the presence of command hallucinations, particularly if the content of their hallucinations suggests indecisiveness, dependency on the hallucinations, and increased self-worth as a result of the hallucinations but little positive relationship with the hallucinations.

There were no significant differences among the three groups on the GAS, on which patients generally manifested severe impairment (mean±SD scores= 38.86±11.84 for command hallucination group, 44.12±13.15 for noncommand hallucination group, and 49.25±16.90 for nonhallucinatory group; F= 2.80, df=2, 62, p=0.07). Composite scores for the Social Behavior Rating Schedule suggested at least some impairment in many areas of interpersonal functioning but no significant differences among the three groups (scores=3.95±2.72 for command hallucination group, 4.21±2.37 for noncommand hallucination group, and 3.23±1.92 for nonhallucinatory group; F=0.65, df=2, 49, p=0.52). Predictably, the Hallucination Predisposition Scale evidenced significant differences, with greater severity for hallucinating patients (scores=5.53±3.23 for command hallucination group and 6.19±2.00 for noncommand hallucination

group) than for nonhallucinating patients (score= 2.75±1.82) (F=7.29, df=2, 40, p<0.01).

DISCUSSION

Command hallucinations appear to have considerable influence in terms of both content, which is often criminal, and their ability to exert control over patients' actions. Perhaps most disturbing is the capacity of these hallucinatory commands to exact unquestioning obedience, often on a frequent basis. There seems little doubt, at least within a forensic population, that command hallucinations play a prominent and disabling role in the day-to-day functioning of chronic patients. Further to this point, we found that many patients respond defensively to clinical inquiries about command hallucinations and tend to deny and minimize their effect. Although two prospective patients had to be excluded from the study because of feigned command hallucinations, nearly one-half were successful at hiding their symptoms from the assessment team. Clinicians are confronted with two difficult tasks: accurately identifying those with hallucinatory commands and assessing the relevance of these commands on a longitudinal basis, either retrospectively in the assessment of criminal responsibility or prospectively in the development of treatment plans.

The study has practical implications in its creation of nonpsychotic indicators to alert clinicians to the possibility of command hallucinations. Pending cross-validation in other clinical settings, the presence of self-reproach/guilt or other identified variables may serve as a preliminary threshold model that might signal the need for a full clinical investigation of command hallucinations. In this regard, we found the SADS and Larkin's Content of Hallucinations Scale to be the most useful in evaluating command hallucinations. Neither of these standard measures, however, replaced relaxed and nonthreatening diagnostic interviews in which a broad range of perceptual disturbances could be explored. Particularly valuable were clinical inquiries, noncommittal in their style, regarding directions received, orders given, and demands imposed by auditory hallucinations.

Unlike Hellerstein and associates (2), we examined command hallucinations extensively through the use of standardized measures. Reliance solely on clinical records would appear to provide an underestimate of the prevalence of command hallucinations, although we do not have sufficient data to gauge the degree to which they are underestimated. Our conclusions offer little comfort to clinicians, on three grounds: roughly one-third of hallucinating inpatients are likely to have command hallucinations (1, 2); a substantial number of patients actively deny them and remain undetected by the assessment team; and, at least in the forensic population, obedience to command hallucinations may have a substantial influence on antisocial behavior.

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Physiological Evidence of Exaggerated Startle Response in a Subgroup of Vietnam Veterans With Combat-Related PTSD

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One of the diagnostic criteria for posttraumatic stress disorder (PTSD) is an exaggerated startle response; however, this phenomenon has not been verified empirically. The authors compared 20 Vietnam combat veterans with PTSD and 18 combat veterans without PTSD on the eyeblink reflex electromyographic response of the startle reaction. Subjects in both groups who failed to show an eyeblink response to the startle stimuli were eliminated from further analyses. Among the remaining subjects, the 13 with PTSD had a significantly greater startle response amplitude than the 12 control subjects at intermediate intensities of acoustic stimuli. The relationship between startle responsivity and both negative and positive symptoms was also investigated.

(Am J Psychiatry 1990; 147:1308–1312)

The introduction of posttraumatic stress disorder (PTSD) into the psychiatric nomenclature was accompanied by conflicting opinions over the validity of the diagnosis. Now, nearly 10 years later, PTSD remains in the diagnostic nosology (*DSM-III-R*), and there is evidence that Vietnam combat veterans may be at high risk for developing the disorder (1). Empirical studies suggest that there are significant differences between veterans with PTSD and both psychiatric control groups (2) and veterans who have had equal exposure to combat but have not sought psychiatric help (3). In general, these findings suggest that the development of chronic PTSD may be influenced by the veteran's degree of combat exposure, substance abuse, and experience of adverse events upon returning to the United States. Furthermore, in reviewing research on the MMPI and combat-related PTSD, Penk et al. (4)

found a relatively high degree of consistency in MMPI profiles across varying samples of subjects. Thus, a considerable amount of evidence has been accumulated in support of the overall validity of PTSD as a diagnostic entity. Much of this evidence, however, is based on self-report measures.

One of the critical symptom clusters necessary for a diagnosis of PTSD involves the persistent presence of increased arousal. Specific criterion symptoms are difficulty sleeping, irritability/anger, difficulty concentrating, hypervigilance, exaggerated startle response, and physiological reactivity upon exposure to events or thoughts similar to those during the traumatic event (*DSM-III-R*). The last two criteria are particularly important because they can be confirmed without using self-report measures. Furthermore, the first three criteria overlap considerably with symptoms of major depressive disorder.

Increased physiological reactivity to events or thoughts relating to the trauma in PTSD has been well researched. There is well-documented evidence of higher heart rate, skin conductance, blood pressure, respiration, and electromyographic (EMG) activity under conditions of reexposure in PTSD patients than in control subjects (5–8). Kolb (9) hypothesized that these results suggest the possibility of a subgroup of combat veterans who suffer from a chronic form of PTSD characterized by persistent conditioned emotional responsivity and perceptual abnormalities. Further evidence supporting this idea was reported by Mueser and Butler (10), who identified a small subgroup of chronic PTSD patients who manifested auditory hallucinations in the absence of other evidence of a psychotic process. These patients also reported significantly greater amounts of arousal than did nonhallucinating PTSD patients. While considerable effort has been directed toward verifying increased physiological reactivity, remarkably little work has been directed toward validating the presence of exaggerated startle responses in PTSD.

Landis and Hunt (11) reported that the human startle response can be reliably and validly measured by monitoring the amplitude of eyeblinks elicited by acoustic stimuli, the eyeblink being the major measurable component of the startle reflex in human beings. Other researchers have verified eyeblink amplitude as a

valid measure of startle responsivity (12, 13) and pointed out this measure's methodological advantages (14). Additionally, evidence has suggested that the eyeblink startle reflex in response to acoustic tones may be associated with affect and is relatively independent of generalized arousal at the time of measurement (15).

Given that an apparently valid and reliable physiological measure of startle reactivity exists, use of this measure would appear to be an excellent way in which to empirically verify exaggerated startle responses in persons with chronic combat-related PTSD. In reviewing the literature, however, we were unable to locate any study that had directly investigated these responses in such subjects. We hypothesized that Vietnam combat veterans with chronic PTSD would exhibit larger eyeblink responses to startling acoustic or tactile (air puff) stimuli than would combat veterans without PTSD. The clinical observations of exaggerated startle responsivity might reflect lowered thresholds for startle rather than increases in the magnitude of responses to normally startling stimuli. Hence, the study was designed also to test the hypothesis that veterans with chronic PTSD would exhibit measurable startle responses at lower sound intensities than those required for eliciting startle responses in veterans without PTSD. We further hypothesized that PTSD patients with exaggerated startle responses would also show evidence of greater perceptual abnormalities.

METHOD

Data were initially collected on 56 veterans screened for potential entry into the study. Eighteen of these veterans were eliminated from the study for one or more of the following reasons: 1) no combat experience, 2) suspected presence of schizophrenia, psychosis, or major affective disorder, 3) history of significant head trauma or other neurological impairment, and 4) inability to provide discharge papers or other independent verification of service in Vietnam. Thus, the remaining 38 subjects had verified service in Vietnam, did not report histories of major neurological disturbance, and did not meet criteria for an additional clinically significant *DSM-III-R* axis I disorder. Additional diagnoses were verified by administrating to all subjects the Schedule for Affective Disorders and Schizophrenia—Change Version (SADS-C) (16). Each subject was also rated with the Scale for the Assessment of Negative Symptoms (17) and the Scale for the Assessment of Positive Symptoms (18).

All of the subjects were nonhospitalized men recruited from a local veterans' center who were tested after they responded to an advertisement for research volunteers. The entire procedure lasted 2–3 hours, and each subject was paid $5 per hour for participation. Descriptive data concerning the subjects' characteristics are presented in table 1.

Of the 38 veterans who met the inclusion criteria for the study, 20 met the *DSM-III-R* criteria for chronic

TABLE 1. Characteristics of Combat Veterans With and Without Diagnoses of PTSD Who Were Tested for Startle Response

Characteristic	PTSD Subjects (N=20)			Control Subjects (N=18)		
	N	Mean	SD	N	Mean	SD
Age (years)	—	40.2	3.3	—	40.9	4.4
Education (years)	—	13.6	2.2	—	13.3	2.2
Unemployed	14	—	—	9	—	—
Race/ethnicity						
Black	4	—	—	1	—	—
Hispanic	1	—	—	1	—	—
White	15	—	—	16	—	—
Service branch						
Marines	9	—	—	3	—	—
Army	9	—	—	9	—	—
Navy	1	—	—	5	—	—
Air force	1	—	—	1	—	—
Months in Vietnam	—	15.4	7.8	—	13.2	8.3
Self-report on current alcohol use (1–9, Likert scale)	—	2.6	2.2	—	2.8	2.1

PTSD that was clearly combat-related. The other 18 were used as control subjects because they did not have diagnoses of PTSD. Diagnoses were made by the first author on the basis of clinical interviews and the subjects' responses to a PTSD symptom checklist (2). At the time of diagnosis, the first author was blind to the startle and other symptom variables.

As an independent check on diagnostic validity, the subjects also completed the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder (19). The groups were significantly different on this measure in the expected direction (mean±SD score=119.94± 14.30 for the PTSD subjects and 88.30±8.95 for the control subjects; t=7.2, df=36, p<0.001). The PTSD group also had a significantly higher mean±SD score on the Vietnam Combat Exposure Scale (20) than the control group (PTSD group, 5.80±0.75; control group, 3.89±1.05; t=6.3, df=36, p<0.001). This finding was not unexpected, as degree of combat exposure is highly predictive of PTSD symptoms in Vietnam veterans (2).

All subjects were given a brief hearing test with a Saico SCR-2 audiometer to ensure that their auditory abilities were intact. For the startle response measurement, after the subject was seated comfortably, two Beckman miniature silver/silver chloride electrodes were positioned below and to the right of his right eye, over the orbicularis oculi muscle. Electrode placement was selected so as to minimize potential electro-oculograph (EOG) artifact. Specifically, one electrode was positioned 1 cm lateral to and ½ cm below the lateral canthus, and the other electrode was placed 1½ cm below and slightly medial to the first electrode. Placement was such that the electrodes were equidistant from the center of the eye and as close to each other as possible; Beckman adhesive collars were used. Additionally, recorded EMG activity was high-pass filtered (1–1,000 Hz) to minimize EOG artifact. A 60-Hz notch filter was also used to eliminate 60-Hz interference. A ground electrode was placed behind the right

ear over the mastoid. EMG activity recorded by the electrodes was directed through a custom-made EMG amplifier (21) to a computerized startle response monitoring system (SR-LAB, San Diego Instruments, Inc.) for digitization and analysis. The system permanently recorded 250 1-msec readings starting at the onset of the startle stimulus. The software parameters by which voluntary and spontaneous eyeblinks were recognized and excluded have been described in detail elsewhere (13). The magnitude of each startle response was defined as the largest of the peak values beginning between 20 and 80 msec after the onset of the startle stimulus, expressed in digital units (each unit=15 μV).

Acoustic startle stimuli were presented binaurally through Telephonics (model TDH-39-P) headphones. Each test session began with a 5-minute acclimation period consisting of 70-dB(A) broadband noise, which continued throughout the session. The session had two components, one acoustic and one tactile. In the first component, seven different trial types were presented in a pseudorandom order, each trial type occurring six times. Although the order of trials was randomized within each subject's test session, it did not vary across subjects. Thus, all subjects were tested under identical conditions. Six of the trial types presented 40-msec noise bursts at different sound levels: 85, 90, 95, 100, 110, and 116 dB(A). The seventh trial type presented a 20-msec burst of 85-dB(A) noise (prepulse) 120 msec before the 116-dB(A) startle stimulus. Such a prepulse stimulus normally inhibits the response to a subsequent startle stimulus, a phenomenon referred to as prepulse inhibition (12); it was included as a confirmatory test of the subjects' ability to detect the relatively weak 85-dB(A) stimulus. The background noise and acoustic stimuli were generated by the SR-LAB system and measured with a calibrated Quest sound pressure level meter (model 215). Sound level was calibrated on a monthly basis by means of a 6-cc coupler in an artificial ear (model EC-9A) and continuous noise.

In the second component of the session, 30-psi air puffs (40 msec in duration) were presented to the subject's neck through a small rubber tube. A total of 30 air puff trials were presented. Air pressure delivery was regulated at the air supply. The internal tube diameter was 4 mm, and the end of the tube was placed approximately 5 mm from the subject's suprasternal notch. On 10 of these trials, the 85-dB(A) prepulse stimulus was presented 120 msec before the air puff. Again, all subjects were tested under identical conditions during this component. The interval between trials in both components varied from 9 to 23 seconds, with a mean interval of 15 seconds.

As in other studies of human startle response (22), in some subjects in each group there was a relative lack of eyeblink EMG activity elicited by the startle stimulus. Therefore, the subsequent analyses of startle data did not include data from these subjects. The criterion for inclusion in the subsequent analyses was an eyeblink EMG amplitude of 8 units or more in the 116-dB(A)

FIGURE 1. Startle Response Reactivity in Subjects With Combat-Related PTSD and in Control Subjects

□ Control group (N=12)
▨ PTSD group (N=13)
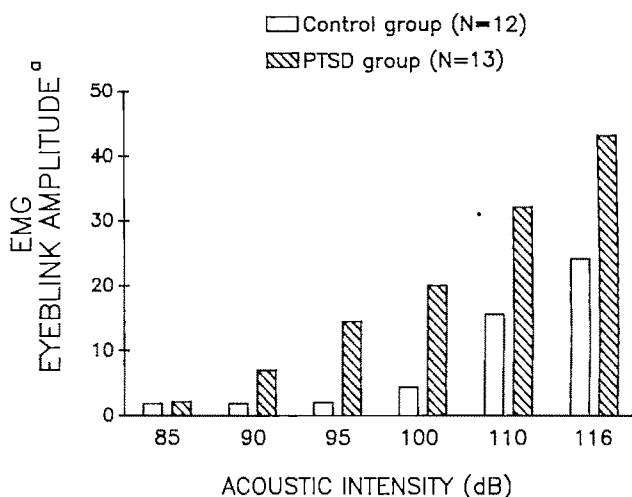
ᵃExpressed in digital units (1 unit=15 μV).

condition. Thirteen (65%) of the 20 PTSD subjects and 12 (67%) of the 18 control subjects were responders, suggesting no appreciable differences between groups in responsivity to the startle paradigm.

RESULTS

For the 25 responders, eyeblink EMG amplitudes for the six different acoustic intensities were analyzed by the nonparametric Mann-Whitney U test, as variances were quite heterogeneous across the PTSD and control groups. Startle reactivity data for the two groups are presented in figure 1. The two groups were not significantly different in eyeblink EMG amplitude in the 85-dB(A) and 90-dB(A) conditions, but the PTSD group exhibited significantly higher eyeblink EMG amplitudes than the control group at 95 dB(A) (U=123, N=25, p=0.01) and 100 dB(A) (U=124, N=25, p=0.01). While the PTSD group continued to manifest higher EMG amplitude than the control group in the 110-dB(A) and 116-dB(A) conditions, these differences did not achieve significance at the designated alpha criterion of p=0.01 (corrected for familywise error rates). The 85-dB(A) prepulse effectively reduced the startle response to the subsequent 116-dB(A) stimulus in both the PTSD and control groups; mean± SD=65.0%±28.9% and 40.0%±86.7%, respectively. Within each group, these amounts of prepulse inhibition were statistically reliable (binomial probability, p<0.001). The two groups did not differ significantly on this measure of prepulse inhibition.

In the second component of the test session, no significant differences were found between the two groups of subjects in their response to tactile startle stimuli. In this component only two subjects in each group were nonresponders (i.e., eyeblink EMG ampli-

tude<8 units, or 120 μV, in response to the air puffs). For the remaining subjects, the mean±SD responses to the 20 tactile trials were 32.6±32.1 and 32.4±23.5 units for the PTSD and control groups, respectively. Comparable results were found when only the subjects who were responders in the acoustic component were examined (PTSD group, 41.5±33.7 units; control group, 33.5±26.1 units). Similarly, both groups exhibited robust amounts of prepulse inhibition: the 85-dB(A) prepulse inhibited the response to the air puffs by 63.4%±29.2% in the PTSD group and 41.6%± 38.8% in the control group (binomial probability for each group, p<0.01). These group means did not differ significantly.

Within the PTSD group, the acoustic startle responders and nonresponders were compared on the Scale for the Assessment of Negative Symptoms to determine whether nonresponsivity to the startle paradigm was associated with negative symptoms such as greater levels of emotional numbing, withdrawal, and affective blunting. This difference approached significance (U=71, N=25, p=0.04), with the responders showing evidence of more negative symptoms (mean± SD=13.9±11.0) than the nonresponders (4.9±4.2). The difference between the acoustic startle responders and nonresponders also approached statistical significance (U=69, N=25, p=0.07) on the Scale for the Assessment of Positive Symptoms, with the responders having a higher mean±SD score (8.4±6.4) than the nonresponders (2.9±3.9), indicating greater levels of perceptual aberration and atypical thought.

DISCUSSION

The results of this study provide empirical evidence for increased startle reactivity in a subgroup of veterans with chronic, combat-related PTSD. It appears that the startle threshold for acoustic stimuli may be reduced in PTSD. The significant differences between the PTSD and control groups were found with 95- and 100-dB(A) acoustic stimuli; neither lower nor higher intensities resulted in statistically reliable differences in startle response magnitudes. There was a trend, however, for the PTSD group to respond with exaggerated responses to the more intense acoustic stimuli. With tactile stimuli, the two groups exhibited virtually identical startle response magnitudes. This unexpected result may be a reflection of stimulus-specific increased startle reactions in persons with combat-related PTSD. This interpretation has clinical appeal, since many veterans report that auditory stimuli, such as an automobile "backfire," will result in an exaggerated startle response. An alternative hypothesis, however, may be that as the strength of the eliciting stimuli increases, all subjects begin to show exaggerated startle responses. Thus, nonsignificant differences between the groups on the relatively strong tactile stimuli may be consistent with the lack of statistically significant differences in response to the more intense acoustic stimuli. Fur-

ther research will be required in order to address these possibilities.

In both the acoustic and tactile components of the test session, an 85-dB(A) prepulse stimulus was effective in inhibiting the startle response. These results confirm that there was no difference between groups in subjects' ability to perceive and respond to the 85-dB(A) noise bursts. Although we had screened all subjects for hearing difficulties, the demonstration of prepulse inhibition confirms the sensitivity of the subjects to stimuli that were qualitatively similar to those used to elicit startle responses in the same test session. Hence, the differences in the responses of the PTSD and control groups to 95- and 100-dB(A) stimuli are unlikely to have been due to differences in hearing thresholds. More detailed analyses using larger samples and startle responses in a measurable physiological paradigm such as ours will be needed to confirm the specificity of the apparent change in acoustic startle response threshold. It is too early to state whether the measure we used will have diagnostic utility, although the results are encouraging. Before criterion cutoff levels of startle reactivity can be determined, we need to extend the database and cross-validate the findings of this study. Nevertheless, our results provide initial evidence to support the exaggerated startle responses reported by many patients with combat-related PTSD.

In addition to the data on startle reactivity, the issue of responsivity to the startle paradigm in PTSD may be of interest. Research on unmedicated schizophrenic subjects (23) has suggested that physiological nonresponsivity to measures such as skin conductance tends to be associated with more negative symptoms (e.g., affective blunting, social withdrawal). To the extent that nonresponsivity on the startle paradigm might mirror other physiological modalities, PTSD appears to be characterized by a converse phenomenon. Specifically, the PTSD subjects in this study who were responders tended to have a greater degree of negative symptoms than the nonresponders. It should be noted that the responders and nonresponders were not significantly different on other variables, including self-report about substance abuse.

The fact that the PTSD responders manifested an exaggerated startle response and a strong trend toward more positive symptoms (e.g., perceptual aberration, atypical thought) is quite consistent with Kolb's hypothesis (9) that a subgroup of patients with chronic, combat-related PTSD have persistent emotional hyperresponsivity and perceptual abnormalities. Kolb also proposed that central adrenergic overactivity might mediate these symptoms, and our results provide indirect support for this possibility. Certainly, central catecholaminergic neurotransmitters have been implicated in the modulation of startle reactivity in animal studies (24, 25). Our inferences, however, assume that startle responsivity is correlated with other indexes of physiological responsivity. This is a speculation that needs empirical verification. The relationship between physiological variables and symptom clusters in PTSD

appears to be complex, but our results suggest that this relationship may be meaningful. Continued data collection, including neurotransmitter metabolite measurements, may be fruitful.

Several cautions should be raised regarding our results. We purposely restricted the number of statistical comparisons and raised the alpha level to help compensate for familywise error rates. Nevertheless, the sample size was modest, and the results need to be replicated. Additionally, we attempted to ensure that our control group had been exposed to combat, and all subjects reported some degree of combat involvement. The PTSD group, however, had significantly greater combat exposure than the control group, and this remains a potential confounding factor. As our work has progressed, we have also become increasingly dissatisfied with simple self-report about substance abuse; thus, we do not think that questions of how alcohol and other drug abuse might have influenced our results were adequately addressed. More sophisticated and detailed measures of substance abuse are needed to answer these questions.

Finally, we are again struck by the apparent high base rates of PTSD in Vietnam combat veterans who are not psychiatrically hospitalized. In this study approximately 50% of the subjects met the *DSM-III-R* criteria for PTSD. Previous studies (3, 26) have also documented the high prevalence of PTSD in outpatient and nonpsychiatric veterans. It is important to attempt to collect information on Vietnam veterans with high combat exposure who do not have PTSD to fully understand etiological factors in this disorder.

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Left Prefrontal Glucose Hypometabolism in the Depressed State: A Confirmation

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The resting-state cerebral metabolic rates for glucose of 10 severely depressed patients (seven bipolar and three unipolar) were compared, before and after treatment with tricyclic antidepressants, to those of 10 control subjects of similar age by means of positron emission tomography and the fluorodeoxyglucose method. Significant left-right prefrontal asymmetry was present in the patients before but not after successful treatment, suggesting that medication can reduce this asymmetry. Also, significant hypofrontality and whole-cortex hypometabolism were found in the patients in the depressed state and persisted in the treated state, despite clinical improvement, suggesting that these abnormalities are not state dependent.

(Am J Psychiatry 1990; 147:1313–1317)

R ecently, a reduction in prefrontal cortex relative glucose metabolism, consistently found in the left dorsal anterolateral prefrontal cortex, was reported in a study of three types of depression with positron emission tomography (PET) (1). A significant increase in relative metabolism was found in the left dorsal anterolateral prefrontal cortex, but not in the right, after successful treatment of depression. The same investigators had previously pointed out (2) whole-brain hypometabolism in bipolar depressed patients and left frontal hypometabolism in a subgroup of unipolar depressed patients; these modifications tended to diminish in the euthymic state. Other authors have reported bilateral relative hypofrontality in bipolar depressed patients (3), relative hypometabolism of the caudate nuclei in unipolar depressed patients (2, 3), and relative hypometabolism in the right temporal lobes of patients with affective disorders (4). Such pioneering studies need to be replicated.

These findings of 1) reduction in left prefrontal metabolism, 2) relative hypofrontality, 3) whole-brain hypometabolism, and 4) relatively lower metabolism in the striata and temporal regions were taken as our basic hypothesis. To try to replicate these results, we undertook a study of severely depressed patients with the PET and [^{18}F]fluorodeoxyglucose method. Patients were studied first in the depressed state and then after they had been treated with the usual tricyclic antidepressants.

METHOD

Subjects

The inclusion criteria for the study were 1) age between 25 and 70 years, 2) presence of a major depressive episode according to *DSM-III* criteria, and 3) a score of less than −20 on the Newcastle Depressive Scale (5) and a score of more than 21 on the Montgomery and Asberg Depression Rating Scale (6). The exclusion criteria were 1) ECT in the previous 12 months, 2) pregnancy or a postpartum depressive episode, and 3) substance abuse. The protocol was approved by the ethical committee of the French atomic energy commission, and informed consent was obtained in all cases.

Ten depressed inpatients (five men and five women), whose mean±SD age was 49±15 years, were selected after their admission to a hospital psychiatric department. Seven patients fulfilled the *DSM-III* criteria for bipolar disorder, depressed, and three for major depression, recurrent. All of the patients were considered to be right-handed on the basis of information from a laterality questionnaire (7). Of the 10 patients, eight met the *DSM-III* criteria for melancholia.

The mean±SD scores on the clinical scales, rated by two psychiatrists (J.-L.M. and P.H.) on the day of the first PET study, were −32.30±8.52 on the Newcastle scale, indicating an "endogenous" depressive episode, and 56.60±6.00 and 36.40±6.55, respectively, on the Hamilton Rating Scale for Depression (National Insti-

tute of Mental Health 1967 version, 26 items) and the Montgomery and Asberg scale, indicating severe depressive symptoms.

As a prolonged drug washout is not ethical in managing severely depressed patients, the first PET study was performed within 5 days after the patients were included in the protocol. At the time of the first PET study, five patients were receiving benzodiazepines (clorazepate, 40–150 mg/day); one patient was receiving clomipramine, 200 mg/day, and chlorpromazine, 50 mg/day; and one patient was receiving viloxazine, 500 mg/day. Three patients had interrupted a previous inefficient tricyclic treatment for at least 8 days.

At the time of the second PET study, all patients had been treated in the psychiatric department for a mean±SD of 4.5±1.2 weeks. Seven patients received amitriptyline, 100–200 mg/day, and three patients received clomipramine, 150–225 mg/day. Because of clinical conditions, other medications were allowed: six patients received clorazepate, 20–50 mg/day; two patients received temazepam, 10 mg/day; and one patient received bromazepam, 9 mg/day.

Depressive symptom ratings on the day of the second PET study were significantly lower, indicating successful treatment: the mean±SD Hamilton depression score was 32.30±11.45 (t=5.94, df=18, p<0.001), and the Montgomery and Asberg depression scale score was 11.20±13.52 (t=5.30, df=18, p<0.001).

The patients were compared to 10 normal control subjects (six men and four women), all right-handed (7), recruited from the hospital staff. Their mean±SD age (38±11 years) was not significantly different from that of the patients (t=1.64, df=18, n.s.). The control subjects were screened with a physical examination, laboratory chemistry studies, and a psychiatric interview. All were free of physical or psychiatric problems.

PET Methodology

Regional cerebral metabolic rates for glucose, expressed in milligrams per 100 milliliters per minute, were measured with the [18F]fluorodeoxyglucose technique applied to PET according to a method described elsewhere (8). PET studies were performed with a LETI TTV01 positron camera, which provided seven simultaneous cerebral slices parallel to the orbito-meatal line with in-plane resolution and a slice thickness of 13 mm, full width, half-maximum. The subjects were studied while they were at rest, with their eyes closed and their ears unplugged. Their heads were positioned in the head holder with reference to a laser beam system. Measurements of the head-holder position and of the subject's head with respect to the laser beams were recorded to ensure accurate repositioning in the second study.

A three-step standardized procedure was applied for regional PET data analysis. The first two steps—selection of the planes and the regions-of-interest positioning procedure—were performed blind to the subjects' condition and have been previously described (8). In

addition, the regions of interest defined on each plane of a subject's first scan images were transferred automatically to the matching plane of the second scan images.

The third step was the definition of cortical functional regions. Using an atlas (9), we assigned an anatomic location to each region of interest in a given plane, so that data from several regions of interest in different planes thought to belong to the same functional cortical area could be pooled (figure 1). Only a few circular regions of interest remained unused; the reliability of their cortical assignment was questionable. The functional cortical regions defined were 1) the prefrontal region, including the heteromodal cortex of Brodmann's areas 9–12 and 44–46; 2) the mediofrontal region, including the anterior cingulate gyrus; 3) a temporal region, including Brodmann's areas 21 and 22; 4) an auditory temporal region (areas 41 and 42); 5) a sensorimotor region, including the middle inferior parts of Brodmann's areas 1–4 and 6; and 6) a posterior parietotemporo-occipital region, including Brodmann's areas 39 and 40 and the adjacent parts of areas 19 and 37.

Statistical Analysis

According to the hypothesis we formulated, the following variables were tested: ratio of right-to-left metabolic rates for glucose in the prefrontal and temporal regions, bilateral normalized metabolic rates (ratio of region to whole cortex) in the whole frontal, striatal, and temporal regions, and whole-cortex metabolic rates. For each variable, the control group was compared to the patients, in both the depressed and the treated states, by means of two-tailed Dunnett t tests. When one of the selected variables was found to differ significantly between the control group and the patient groups, we subsequently used a one-tailed paired t test to compare this variable in the patients when depressed and when treated, since the results of the previous comparison to the control subjects, which were consistent with the hypothesis based on the literature findings (1–4), established clear expectations about the direction of the changes from the depressed state to the treated state.

All statistical comparisons were performed using the BMDP statistical package (10) on a VAX 8350 computer.

RESULTS

For the prefrontal cortex, the right-left ratio of the patients when depressed (mean±SD=1.02±0.03) was significantly different from that of the control subjects (0.99±0.01) (Dunnett's test, p<0.05) and from that of the patients when treated (0.99±0.03) (paired t=1.90, df=9, p<0.05). There was no difference between the control subjects and the treated patients (Dunnett's test, p=1.00). The higher right-left prefrontal cortex

FIGURE 1. Projection of Regions of Interest in a Study of Cerebral Metabolic Rates for Glucose on a Cytoarchitectural Map of the Convex Surface of the Human Cortex According to Brodmann[a]
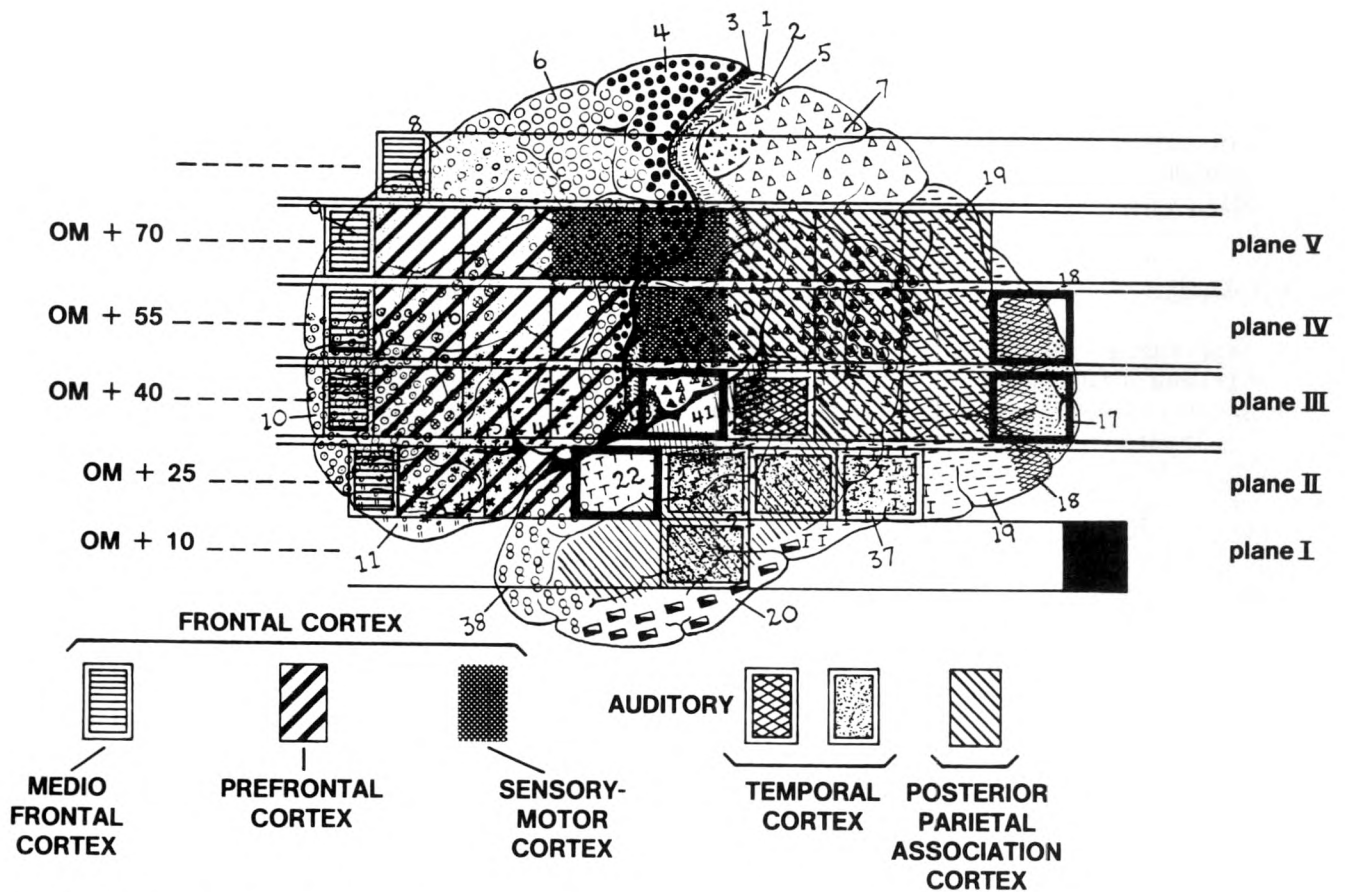
[a]OM=orbitomeatal line (+10 mm, +25 mm, etc.).

ratio in the depressed patients was due to lower metabolism in the left prefrontal region (mean±SD regional cerebral metabolic rate for glucose=4.53±0.93 mg/100 ml per minute) than in the right (4.65±0.94 mg/100 ml per minute). Moreover, the absence of asymmetry in the prefrontal cortex in the treated state was due to an increase in metabolism from that of the depressed state, more marked in the left prefrontal cortex (4.87±1.18 mg/100 ml per minute) than in the right (4.84±1.10 mg/100 ml per minute).

No significant right-left asymmetry was found in the temporal cortex. The mean±SD right-left ratio for the temporal cortex was 1.00±0.04 for the control subjects, 1.00±0.04 for the patients in the depressed state, and 1.00±0.07 for the patients in the treated state.

Normalized whole frontal metabolism was significantly lower in the patients, both in the depressed state (mean±SD=1.01±0.02) (Dunnett's test, p<0.05) and in the treated state (1.00±0.02), than in the control subjects (1.04±0.02). There was no significant difference between the two states of the patients (paired t=−1.07, df=8, p=0.15).

No significant difference in normalized metabolic rate for glucose was found in the striatal and temporal

regions. The normalized rate for the striatal regions (mean±SD) was 1.09±0.08 in the control subjects and 1.15±0.16 and 1.09±0.12 for the patients in the depressed and treated states, respectively. In the temporal regions, the rates were 0.91±0.03 in the control subjects, 0.94±0.04 in the patients when depressed, and 0.94±0.04 in the treated patients.

Finally, the mean±SD whole-cortex metabolic rate for glucose was lower in the patients both in the depressed state (4.58=0.94 mg/100 ml per minute) (Dunnett's test, p<0.01) and in the treated state (4.88±1.10 mg/100 ml per minute) (Dunnett's test, p<0.05) than in the control subjects (6.41±1.30 mg/100 ml per minute). There was no difference between the patients when depressed and the patients when treated (paired t=1.10, df=9, p=0.15).

Correlations between clinical scores and regional metabolic rates were subsequently investigated through stepwise regression analysis. We searched for correlations of scores with the left prefrontal cortex metabolic rate, as the increase of metabolism in this region accounted for the disappearance of the prefrontal asymmetry observed in the patients from the depressed to the treated state. Because of the small size of the sample, searching for all

possible correlations was not possible without encountering a high probability of type I error. On the basis of these considerations, we made an a priori selection of a limited number of clinical scores to use in the analysis (from the Hamilton scale: slowness, mood, ideas of suicide, and total score; from the Montgomery and Asberg scale: weariness, concentration difficulties, sadness, and total score). A significant correlation was observed for the Hamilton ideas of suicide score (r=0.60, df=8, p<0.04).

DISCUSSION

Because of the intensity of the depressive symptoms in our patients, a complete drug washout was impossible and would have been unethical. This was balanced by the opportunity to study severely depressed patients, unlike other studies, where drug-free patients could be studied but were in only a moderately depressed state (1, 2).

The influence of the psychotropic medications on the whole-cortex metabolic rate at the time of the first PET study cannot be entirely ruled out, but the five patients receiving benzodiazepines at that time did not differ significantly from the other five patients, either in whole-cortex metabolic values (mean±SD=4.32± 1.28 and 4.32±0.47 mg/100 ml per minute, respectively) (t=0.85, df=8, n.s.) or in whole frontal normalized values (1.01±0.02 and 1.01±0.02 mg/100 ml per minute, respectively). Furthermore, we know of no PET study that has reported prefrontal asymmetry related to chronic treatment with psychotropic drugs. Also, other investigators have found a different distribution of cerebral metabolism related to benzodiazepine treatment than the distribution we observed in our patients. Buchsbaum et al. (11) pointed to a decrease in glucose metabolic rate in the posterior cortical regions and a relative increase in the basal ganglia during clorazepate treatment. Mathew et al. (12) observed a decrease in right hemisphere cerebral blood flow after acute administration of diazepam to normal volunteers, but in our study we observed left-right relative hypometabolism in the depressed state, and the disappearance of this frontal asymmetry in the treated state was due to an increase in glucose utilization in the left prefrontal region and not to a decrease in the right prefrontal region, which would have been expected if there had been only an effect of benzodiazepines. Moreover, Sackeim et al. (13) recently reported a reduction in global cortical blood flow in depressed subjects that they could not attribute to benzodiazepine treatment.

Another methodological point is the test-retest variability, which was not explored in our control subjects for practical and ethical reasons. However, the coefficient of variation of the right-left regional metabolism ratios in our control group was found to be 2%, meaning that the test-retest intrasubject variability had to be smaller than 2% in the control subjects. Based on pa-

tients' data, and assuming no treatment effect on regional metabolism rate in the temporal cortex, the test-retest intrasubject variability of the right-left ratio in the temporal cortex was found to be 0.5%. This variability includes errors due to repositioning.

Nevertheless, our findings, obtained from a small sample of screened depressed patients, agree with those of several previous PET studies of depressed subjects. First, the left-right relative asymmetry of the prefrontal cortex found in the patients in this study during the depressive state, and reversible in the treated state, is a finding interestingly analogous to the temporary reduction of left dorsal prefrontal cortex glucose metabolism in depressed subjects recently pointed out by Baxter et al. (1). Such results actualize the theories of cerebral hemisphere functioning in depression (14) and would denote a decrease in the analytic and organizing abilities of the left prefrontal regions during the depressive state. The correlation that we observed between left prefrontal metabolic rate and score on the ideas of suicide item on the Hamilton scale must, however, be considered with caution in so small a sample and needs replication before any definitive conclusion can be drawn.

Our finding of normalized whole frontal cortex hypometabolism in our patients is congruent with the findings of Mayberg et al. (15) and with the results of Baxter et al. (1) and Buchsbaum et al. (3). In addition, the whole-cortex absolute hypometabolism we observed is comparable to the findings of Baxter et al. (2) in bipolar, depressed and mixed, patients and is analogous to the decrease in global cortical blood flow recently reported (13) in 41 depressed patients. However, the whole-cortex absolute hypometabolism persisted in our patients when they were studied in the treated state. Although the metabolic rates for glucose for the whole cortex were slightly higher in the patients when they were treated than when they were in the depressed state, the difference did not reach a significant level. This can be put in perspective by noting preliminary findings (13) that after a course of ECT, further lowering of global cortical blood flow is found in recovering patients. Those findings suggest that clinical recovery is not necessarily accompanied by normalization of the whole-cortex hypometabolism, at least after the psychotropic treatment we used and after treatment with ECT. The relative hypofrontality also persisted in our patients in the treated state.

In conclusion, the data from this study suggest that the disappearance of left-right prefrontal asymmetry from the depressed to the treated state relates to the effects of medication (mainly tricyclic antidepressants) or to clinical improvement. However, the persistence of relative hypofrontality and of whole-cortex hypometabolism do not appear to be state dependent. Consequently, this persistence should be studied with a longer interval between studies in order to determine whether these abnormalities are related to episode or trait factors.

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Platelet MAO Inhibition, Urinary MHPG, and Leukocyte β-Adrenergic Receptors in Depressed Patients Treated With Phenelzine

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The authors investigated three biochemical indices of peripheral catecholamine activity in 36 depressed inpatients treated with the monoamine oxidase (MAO) inhibitor phenelzine. Platelet MAO activity, urinary excretion of 3-methoxy-4-hydroxyphenylglycol (MHPG), and leukocyte β-adrenergic receptor functions were measured before and during the 4th week of phenelzine treatment. There were significant reductions in platelet MAO activity, urinary MHPG excretion, and depressive symptoms in all of the patients. Responders had the same decrease in MHPG as nonresponders. There were no changes in leukocyte β-receptor function in a small subgroup of the patients.
(Am J Psychiatry 1990; 147:1318–1321)

The monoamine oxidase inhibitors (MAOIs) have reemerged as important antidepressants. The inhibition of monoamine oxidase (MAO), partially responsible for the breakdown of neurotransmitters such as norepinephrine and serotonin, presumably produces higher neurotransmitter concentrations in the synaptic cleft near the postsynaptic receptor. We measured the effect of phenelzine treatment on platelet MAO activity, the urinary excretion of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), and the leukocyte β-adrenergic receptor response.

There is consistent evidence that tricyclic antidepressants lower MHPG excretion. Early studies found that pretreatment urinary MHPG levels could predict response to the tricyclic antidepressants; subjects with low MHPG excretion improved when given imipramine, and subjects with normal to high MHPG excretion responded to amitriptyline (1, 2). However, cross-validation studies have yielded mixed results (3). There is limited information from several small-sample studies on urinary MHPG levels predicting response to MAOIs. For example, an early study (4) found that pretreatment MHPG levels were unable to predict clinical response in 12 depressed patients treated with phenelzine, although the patients' urinary MHPG values were markedly lower after 4 weeks of treatment. By contrast, a more recent study (5) found that patients with low urinary MHPG levels (less than 1500 μg/ml) responded better to the MAO-A specific inhibitor moclobemide.

Chronic administration of MAOIs and tricyclic antidepressants produces β-adrenergic receptor downregulation in the rat brain (6). We examined the effects of phenelzine on leukocyte β-adrenergic receptors as measured by the activity of adenylate cyclase in the presence and absence of the agonists norepinephrine (norepinephrine-stimulated adenylate cyclase) and isoproterenol (isoproterenol-stimulated adenylate cyclase). To our knowledge, the effect of MAOIs on the leukocyte β-adrenergic receptor/adenylate cyclase system in humans has not been studied previously.

Our objectives were 1) to examine whether low MHPG levels predicted an antidepressant response to phenelzine, 2) to examine whether the reduction in MHPG excretion produced by phenelzine correlated with clinical response, and 3) to explore the direct effects of phenelzine on the function of the leukocyte β-adrenergic receptor. We studied patients after a drug-free washout period and measured platelet MAO inhibition, urinary MHPG levels, and leukocyte β-adrenergic receptor function at baseline and after a fixed period of phenelzine treatment.

METHOD

Our subjects were 36 depressed patients who required hospitalization for acute exacerbation of their affective illness. Twenty-three of the patients were women, and 13 were men; their mean±SD age was 49.6±15.36 years. After providing informed consent, all 36 patients went through a drug-free washout period in the hospital. For a mean of 15.6±7.2 days all psychotropic medications were stopped, with the ex-

ception of an occasional dose of 500 mg of chloral hydrate. All patients were given a low-monoamine diet. According to Research Diagnostic Criteria (RDC), 27 of the patients had major depressive disorder; four had bipolar disorder, depressed phase; and five had minor depression. Diagnoses were derived by consensus between two trained independent raters using information from all available sources. The 21-item Hamilton Rating Scale for Depression and the Global Assessment Scale (GAS) were also completed by trained raters. Interrater reliability based on total Hamilton scale scores and computed by intraclass correlation coefficient for independent raters was 0.95.

While still blind to biochemical values, we categorized the patients as responders or nonresponders on the basis of a 30% or more improvement from pretreatment in Hamilton scale and/or GAS scores after a minimum of 4 weeks of phenelzine treatment (the Affective Disorders Rating Scale score [7] was used in two patients). There was a significant decrease in depressive symptoms as measured by mean Hamilton depression scale score in all of the patients remaining in the study at the 4th week of treatment (t=2.03, df=30, p=0.05). Fifteen patients were responders (i.e., their mean improvement in Hamilton scale score during week 4 was 38.5%), and 16 were nonresponders (their mean change in Hamilton scale score during week 4 was −7.5%). Responders and nonresponders differed significantly in their pretreatment (23.9 versus 30.9, t=2.64, df=29, p<0.02) and posttreatment (15.5 versus 32.9, t=5.41, df=29, p<0.001) Hamilton scale scores. Thus, responders started with lower scores and improved with treatment, but the more severely depressed nonresponders actually deteriorated after treatment. Responders and nonresponders did not differ in the dose of phenelzine received during the 4th week (50.62 mg/day versus 52.50 mg/day, respectively). Of the five patients with minor depression, two were responders, two were nonresponders, and one did not complete the study, and their pretreatment Hamilton scale scores, reflective of initial severity, did not differ significantly from the scores of the rest of the patients (21.4 versus 28.2, respectively).

After the drug washout period, blood samples were obtained in the morning before breakfast for the measurement of platelet MAO activity and leukocyte β-adrenergic receptor response to norepinephrine and isoproterenol. Twenty-four-hour urine samples were also obtained under close monitoring to ensure a complete collection. These samples were measured for volume, creatinine, and MHPG excretion; incomplete collections were discarded. Phenelzine was administered in an open design with starting doses between 30 and 60 mg/day, which were increased after the first 2 weeks to doses of up to 90 mg/day when tolerated or until MAO inhibition of at least 80% was achieved. Of the 36 patients who entered the study, 32 completed 4 weeks of treatment with phenelzine; their mean±SD dose

during the 4th week was 51.6±10.73 mg/day. Biochemical and behavioral measures were repeated during the 4th week of treatment.

Platelet MAO activity was measured in 35 patients before and 32 patients after treatment, by a modification of a radiometric method using the substrate [^{14}C]tyramine (8). Results are expressed as nanomoles of substrate (tyramine) metabolized per mg platelet protein/hour. Pretreatment platelet MAO activity was significantly greater in women than in men (t=2.7, df=33, p<0.01).

Leukocyte adenylate cyclase (as a measure of β-adrenergic receptor response) was analyzed in 18 patients after isolation of their leukocytes (9). Adenylate cyclase was determined according to the methods described by Pandey et al. (10). Briefly, intact leukocytes were incorporated with [^{3}H] adenine and then stimulated in the presence or absence of norepinephrine or isoproterenol (10^{-4}M). The [^{3}H] cAMP formed was isolated and quantitated, and results are expressed as percent of conversion of total incorporated [^{3}H]-nucleotides to [^{3}H] cAMP. Urinary MHPG was measured by gas-liquid chromatography (11). Adequate samples were obtained in 28 patients before and 23 patients after treatment. MHPG values are given as the total 24-hour excretion as well as a ratio of MHPG to excreted creatinine (MHPG/creatinine).

In addition to computing Pearson product-moment correlation coefficients, we also used partial correlations and probit regression to hold constant the effects of psychotic status on response. Data analyses were also performed after excluding the five patients with minor depression to remove any possible bias from this group. All probability values are two-tailed.

Analysis of data frequently requires a series of estimates (or tests) to examine a particular hypothesis. To ensure an experiment with a type I error rate of 5%, the significance level of each individual comparison or association can be adjusted by using the Bonferroni method. For example, if five statistical tests are performed, to obtain an overall confidence level of 1−a, we must use an individual comparison type I error rate of a/5. The Bonferroni correction is overly conservative and perhaps not meaningful when measures are highly correlated, such as the transformation of MHPG/24 hours to a ratio of MHPG to excreted creatinine or the reanalysis of the same data after excluding a few subjects.

RESULTS AND DISCUSSION

Phenelzine treatment markedly decreased the patients' mean platelet MAO activity from its pretreatment value of 30.4 to 3.61 nmol of tyramine metabolized/mg protein per hour during the 4th week of phenelzine administration (i.e., 88% platelet MAO inhibition). There were no significant correlations be-

TABLE 1. Behavioral and Biochemical Measures in 36 Depressed Inpatients Treated With Phenelzine

Measure	Pretreatment		Posttreatment	
	Mean	SD	Mean	SD
MAO activity (nmol of [^{14}C]tyramine metabolized/mg protein per hour)[a]	30.16	13.60	3.71	2.15
MHPG excretion (µg/ml)[b]	1323.40	718.64	851.65	615.90
MHPG/creatinine ratio[c]	1.45	0.72	0.95	0.69
Norepinephrine-stimulated cAMP production (%)[d]	0.54	0.30	0.60	0.39
Isoproterenol-stimulated cAMP production (%)[d]	0.64	0.36	0.65	0.36

[a]The posttreatment mean value was significantly lower than the pretreatment mean value in the 31 valid pairs (t=11.3, df=30, p<0.001, paired t test).
[b]The posttreatment mean value was significantly lower than the pretreatment mean value in the 23 valid pairs (t=2.94, df=22, p=0.008, paired t test; Bonferroni p=0.02).
[c]The posttreatment mean value was significantly lower than the pretreatment mean value in the 23 valid pairs (t=2.81, df=22, p=0.01, paired t test; Bonferroni p=0.02).
[d]Conversion observed of total incorporated [^{3}H]-nucleotides to [^{3}H] cAMP over the basal activity in the presence of norepinephrine or isoproterenol.

tween pretreatment values of either MHPG or β-adrenergic receptor response and age, sex, duration of washout period, baseline MAO activity, or Hamilton depression scale scores.

Phenelzine induced a significant decrease in the posttreatment urinary MHPG excretion and the MHPG/creatinine ratio (see table 1). When patients with minor depression were excluded, the decrease in urinary MHPG (t=2.50, df=19, p=0.02) and the MHPG/creatinine ratio (t=2.20, df=19, p=0.04) remained significant. These results confirm previous reports demonstrating decreased urinary MHPG excretion in response to MAOI administration (4, 5, 12).

Clinical Relationship of Phenelzine-Induced MHPG Decrease

Decreases in the Hamilton scale scores were not significantly correlated with decreases in either MHPG (r=0.15, N=22, n.s.) or the MHPG/creatinine ratio (r=0.20, N=22, n.s.). This replicates the finding of Beckman and Murphy (4), who found no correlation between decreases in depression ratings and reductions in MHPG. Stefanis et al. (5) did not report specific information on this relationship.

Because we had previously found that psychotically depressed inpatients did not respond to phenelzine (13), we used a probit regression to control for psychotic status and found that even after psychosis was taken into account, response status was still not predicted by the decrease in either MHPG or MHPG/creatinine ratio (χ^2=0.01 and χ^2=0.12, respectively,

df=1, n.s.). Further, when we partialed out the effect of psychotic status, the decrease in MHPG or MHPG/creatinine ratio failed to significantly predict decreases in Hamilton depression scale rating (partial correlations=0.31 and 0.26, respectively).

It is possible that nonresponse to MAOI may be due to mechanisms unrelated to MAO activity. Thus, we may see a correlation between the biochemical effect of MAOIs on MHPG and the degree of clinical change in our group of responders only. Therefore, we examined the responders separately and, indeed, found that the percent decrease in the Hamilton scale score was correlated with the percent decrease in both MHPG (r=0.65, N=10, p=0.04; Bonferroni p=0.24) and the MHPG/creatinine ratio (r=0.71, N=10, p=0.02; Bonferroni p=0.12). In those patients who had the potential to respond to phenelzine, the degree of response at week 4 may have been related to the decrease in MHPG. It is possible that this correlation is significant by chance alone. The finding is reported for completeness in case it becomes relevant in the light of future research. The exclusion of one patient with minor depression (a responder) did not alter the correlation (r=0.65 and r=0.71, respectively).

Pretreatment MHPG as a Predictor of Clinical Response

Pretreatment MHPG did not predict clinical response to phenelzine. Thus, pretreatment MHPG and the MHPG/creatinine ratio were not significantly correlated with percent improvement in Hamilton scale scores (r=0.17, N=23, n.s., and r=−0.01, N=23, n.s., respectively). Further, pretreatment MHPG did not differ between responders and nonresponders (1237 µg/ml versus 1455 µg/ml; t=−0.7, n.s.). Again, when we controlled for the effects of psychotic status, pretreatment MHPG and the MHPG/creatinine ratio consistently failed to predict a decrease in Hamilton scale scores (r=0.46, N=23, p=0.03, Bonferroni p=0.18; r=0.17, N=23, n.s., respectively, partial correlations) or response status (adjusted χ^2=0.7, df=1, n.s., and χ^2=0.5, df=1, n.s, respectively).

When we applied the Bonferroni correction, the one significant finding became nonsignificant, and we conclude that MHPG does not predict clinical response. Thus, our results generally replicate those of Beckman and Murphy (4), who found no difference in pretreatment MHPG between responders and nonresponders (1800 µg/ml versus 1780 µg/ml). When we dichotomized the patients by MHPG excretion, as Stefanis et al. (5) did, we found that those who had less than 1500 µg/ml MHPG excretion before treatment were neither more improved (t=−0.72, n.s.) nor more likely to be responders (χ^2=0.3, n.s.) than patients excreting more than 1500 µg/ml. In contrast, Stefanis et al. (5) did report a better clinical response in patients excreting less than 1500 µg/ml of urinary MHPG. One possible explanation for this difference is that the Stefanis group used the MAO-A specific inhibitor moclobe-

mide. The D-type score, incorporating MHPG, might prove better in predicting clinical outcome (14), but we did not measure all its components. Also, pretreatment MHPG may be more useful in predicting clinical outcome in bipolar depression than in unipolar depression. Our bipolar subgroup of four patients was too small for meaningful analyses.

Effects on Leukocyte β-Adrenergic Receptors

We found no change in the β-adrenergic receptor response before and during the 4th week of phenelzine treatment in patients who had completed these measurements (see table 1). The reverse catecholamine hypothesis suggests that depression is a hyperadrenergic state whose treatment includes the desensitization of the noradrenergic receptor. The lack of change in the leukocyte β-adrenergic receptor in our study does not support a direct action on the leukocyte β-adrenergic receptors by phenelzine and argues against a reverse catecholamine hypothesis (15). The leukocyte β-adrenergic receptor is a surface receptor and does not have the presynaptic component that is associated with postsynaptic receptors in the brain. Thus, it does not share the microenvironment of a neuronal synapse and would not reflect change in brain postsynaptic receptors associated with presynaptic norepinephrine release. This might explain the differences between this study and the down-regulation of postsynaptic β-adrenergic receptors found in rat brain after chronic antidepressant treatment. We have previously reported the effects of phenelzine on I^{125}-cyanopindolol binding of human leukocyte β-adrenergic receptor and have observed no significant changes (16).

We should note that our study, as well as those of Beckman and Murphy (4) and Stefanis et al. (5), used a 4-week treatment period. Because some patients may require more time to fully respond, we think it is important to keep this limitation in mind. Although we prescribed phenelzine in doses up to 90 mg/day (when tolerated), we did not think it was clinically prudent to extend the study because our nonresponders as a group were actually deteriorating after a 2-week washout period and 4 weeks of treatment and would require a 2-week washout from phenelzine before a subsequent drug could be administered.

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Maintenance of Hope in HIV-Spectrum Homosexual Men

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The struggle to maintain hope has been described as a central theme faced by clinicians who work with HIV-spectrum people. The authors investigated psychiatric and psychosocial variables thought to be related to level of hope in a community sample of 208 HIV-positive and HIV-negative homosexual men, with the goal of identifying possible risk and protective factors in the progression of HIV infection. Overall, they found high levels of hope and low levels of current syndromal disorder or depressive symptoms. While the sample was a selected group of successful and well-educated homosexual men, it nevertheless remains noteworthy that they were able to preserve a sense of faith in their future despite HIV infection.
(Am J Psychiatry 1990; 147:1322–1326)

T he struggle to maintain hope has been described as one of the most striking and recurrent themes faced by clinicians who work with HIV-spectrum people (1). Hope (or hopelessness) is believed to be related to psychiatric status (2); endocrine function, as described by Selye (3) and Schmale and Iker (4) in their seminal formulations about stress and illness; and immunologic function in terms of susceptibility to infection (5). Loss of hope is seen in the context of a biopsychosocial interaction to account for such disparate phenomena as rapid death from voodoo, evil eye, and hexes. In our culture, an analogous phenomenon may be the abrupt death of patients after their being told of a fatal prognosis (6).

Hope entails the expectation that something worthwhile lies ahead. It implies confidence in a future event or circumstance that is positively appraised. Measures of hopelessness often inquire about demoralization, a "belief in one's ineffectiveness, engendered by severe life defeat" (7, p. 230). While hopelessness and demoralization often occur together, they are conceptually and perhaps empirically distinct. For terminally ill patients, morale may remain high and hope possible without recourse to denial, although the person's time frame may be foreshortened.

Most studies of the impact of psychological outlook on health status in medically ill people have focused on patients with cancer (8, 9). To date, results have been inconsistent regarding the effect of hope on survival. On the basis of a review of the available literature, Cohen (6) concluded that "a feeling of hope associated with either an increased sense that one can cope (or be helped by others to cope) with the problems with which one is confronted ... may be accompanied by biological changes that enhance physical as well as mental health" (p. 106). In contrast, Cassileth et al. (10) did not find that any of the psychosocial variables they studied, including level of hope, were associated with survival in their study of over 300 patients with advanced cancer. They suggested that hope may have an impact on the progression of illness in earlier stages of disease, although their research did not address this question. In addition, some work in this area with patients with AIDS and AIDS-related complex is beginning to appear, although results are based on small samples (L. Temoshok et al., unpublished data, 1988) or on clinical observations and so are inconclusive (11, 12).

In this context, we investigated personal and social variables that may be related to level of hope in a volunteer sample of HIV-spectrum men. The dimensions that constituted our focus of inquiry were social relationships (social supports and conflicts), life events, and personal qualities (perceived control over one's destiny and sense of commitment). In addition, we were interested in studying level of hope in relation to depressive disorder, depressive symptoms, and overall level of psychological functioning, as well as to HIV serostatus and symptoms. Our overall longitudinal goal is the identification of protective and risk factors in the progression of HIV infection. If hope operates as a protective factor, it would be of value to identify social and psychological conditions susceptible to intervention that may contribute to its maintenance. In this sample of HIV-positive and HIV-negative ho-

mosexual men, we addressed the following questions: 1) Are stressful life events or components of social relationships related to levels of hope? 2) Do hopeful men in this population express a stronger sense of commitment and internalized locus of control? 3) Does loss or significant diminution of hope among seropositive men occur in the absence of clinical depressive disorder? 4) Is level of hope correlated with HIV status and illness state? Where appropriate, we compared responses of subjects with and without HIV infection.

METHOD

Subjects

The study participants were homosexual men who had been tested and informed of their HIV antibody status before entry into the study. They did not have a diagnosis of AIDS or a history of neurological disorder. They volunteered in response to announcements about the study that appeared in newsletters of two local homosexual organizations and to a notice in a commercial newspaper with a homosexual readership.

The present report is based on baseline assessments of 208 participants, the majority of whom will be studied for 5 years. Of these, 124 were HIV seropositive, and 84 were seronegative. This was a largely white, well-educated, and financially successful group of homosexual men. Eighty-seven percent (N=181) were non-Hispanic white. Ninety percent (N=187) had attended at least some college; 62% (N=129) had graduated, and 26% (N=54) had received graduate or professional degrees. The household median annual income was $30,000–$35,000. Both the average and median ages were 38 years (range, 22–59 years). Twenty-eight percent (N=58) were raised Protestant, 50% (N=104) Catholic, 15% (N=31) Jewish, and 7% (N=15) other.

Procedure

Each participant was mailed a packet of self-rating scales 2 weeks before his initial study visit. He was then seen for a full day of assessments, including neurological and medical examinations and blood work (with a confirmatory HIV test), psychiatric, psychosocial, and psychosexual interviews, and neuropsychological tests. All participants gave written informed consent and were paid $10 an hour for their time.

Measures

Hopelessness Scale. Beck and colleagues' 20-item Hopelessness Scale (2) served as the measure of our dependent variable. This self-rating scale with a true-and-false format was designed to "reflect different facets of the spectrum of negative attitudes about the future." Items address feelings about the future (an

affective dimension), giving up, and future expectations (a cognitive dimension). Nine items are keyed "false," and 11 items are keyed "true"; the total hopelessness score is the sum of items keyed in the "hopeless" direction. Low scores signify hope, defined as faith that good times lie ahead and that the respondent continues to have a "fighting spirit." In our study sample, the internal consistency reliability of the overall scale was 0.89.

Social Support Scale. This scale was developed by Wortman (13) specifically to assess several aspects of social support in a Chicago community sample of homosexual men. It includes 28 items representing six dimensions: perceived emotional and material support, subjective and objective social integration, affirmation (e.g., others think "it's all right to feel what you're feeling"), and social conflict. The first five dimensions measure positive aspects of social support and are significantly intercorrelated. Social conflict is inversely correlated with the other five scores, separately and in combination. In our sample the internal consistency reliabilities of the five positive dimensions combined and the seven-item social conflict scale were 0.82 and 0.68, respectively.

Health Locus of Control Scale. This scale, developed by Wallston and colleagues (14), is derived from Rotter's internal-external locus of control studies. The version we used is focused on health status and has 18 items. A sample item is, "if you become sick, you have the power to make yourself well again." Factor scores are generated for the following three measures: internal locus of control, belief that events are influenced by powerful others ("power"), and belief that events are controlled by chance. The power and chance subscales are combined to give a measure of external locus of control. In our sample, the internal consistency reliabilities for the three scales were 0.72, 0.62, and 0.73, respectively.

Commitment Scale. This scale is one of three incorporated by Kobasa (15) in developing her Hardiness Scale and is the one with the most robust psychometric properties (16). Its 16 items were adopted by Kobasa from earlier measures of alienation from self and work. A sample item is, "I often wake up eager to take up my life where it left off the day before." High and low scores are meant to be defined within samples; there are no standard cutoff scores. In our sample, the internal consistency reliability was 0.82.

Life Event Questionnaire. This is a 76-item clinician-administered checklist that inquires about stressful life events in the past 6 months. The items are derived from Dohrenwend's work as modified by Martin (J. Martin, unpublished data, 1985) and ourselves. Respondents are asked to assess the valence (positive or negative) and impact (rated 1 to 3) of each event reported.

Hamilton Rating Scale for Depression. This is the preeminent clinician rating scale currently used for assessing severity of depression in diagnosed patients. We used the 17-item structured interview guide for the

Hamilton depression scale (17). It focuses on the past week. On the basis of broad experience, "mild" depression is defined by scores of 7–12, while scores below 7 are often used as the definition of "recovered" or "not depressed."

Brief Symptom Inventory (SCL-53). This is a 53-item version of the SCL-90, a widely used self-rating scale that provides subscale scores in nine symptom areas focusing on the past week. Each item is scored on a 5-point scale of frequency. The seven items in the depression subscale refer to dysphoric mood, loss of interest, and other nonvegetative symptoms. In our analyses, one item, "feeling hopeless about the future," was omitted when we compared depressive symptoms and hopelessness because of its obvious redundancy. Higher scores signify greater symptoms (18).

DSM-III-R diagnoses. These diagnoses were made on the basis of a structured psychiatric interview (Structured Clinical Interview for DSM-III-R, Axis I) conducted by trained clinicians. We modified it for an HIV sample (19).

HIV Symptom Checklist. On the basis of a physical examination and medical history, a physician (blind to the subjects' HIV status) assessed the presence or absence of 20 physical symptoms and signs commonly but not exclusively associated with HIV infection, such as sore throat, persistent cough, herpes, shingles, and night sweats. It was possible for HIV-negative subjects to get scores above zero. The total score, which was the sum of symptoms present currently or in the past 3 months, ranged from 0 to 20. T cell subsets were also assessed as in index of immune status.

The hopelessness, social support, health locus of control, commitment, and Brief Symptom Inventory scales were completed by subjects. The remainder were administered by trained clinicians (psychiatric and medical) at the baseline visit.

Statistical Analysis

Data were analyzed by means of Pearson correlations, t tests, and multiple regression analyses, both hierarchical and stepwise. All tests were two-tailed. The Bonferroni correction was applied when multiple comparisons were made.

RESULTS

The Wortman Social Support Scale factors were individually and cumulatively correlated with our measure of hope at statistically significant levels. As shown in table 1, higher levels of hopelessness were associated with lower levels of all forms of positive support and with higher levels of social conflict.

Higher scores on measures of internal locus of control and commitment were negatively associated with hopelessness, while beliefs that events are influenced by external forces (powerful other people or chance) were positively related, as shown in table 1.

TABLE 1. Correlations of Psychosocial and Medical Measures of Hopelessness in HIV-Positive and HIV-Negative Homosexual Men

Measure	HIV-Positive Men (N=118)[a]		HIV-Negative Men (N=79)[a]	
	r	p[b]	r	p[b]
Social environmental				
Social support factors				
Perceived emotional support	−0.49	0.000	−0.36	0.002
Perceived material support	−0.40	0.000	−0.09	n.s.
Affirmation	−0.45	0.000	−0.40	0.000
Subjective social integration	−0.49	0.000	−0.41	0.000
Objective social integration	−0.25	0.001	−0.24	n.s.
Social conflict	0.27	−0.003	0.34	0.002
Sum of positive life events	−0.26	0.004	−0.22	0.05
Sum of negative life events	0.11	n.s.	0.17	n.s.
Personal measures				
Locus of control				
Internal	−0.35	0.000	−0.43	0.000
External	0.33	0.000	0.22	0.06
Commitment	−0.61	0.000	−0.53	0.000
Psychological status				
Hamilton depression scale	0.32	0.000	0.42	0.000
Brief Symptom Inventory				
Depression subscale	0.69	0.000	0.42	0.000
Global severity index	0.65	0.000	0.43	0.000
Physical status				
HIV Symptom Index	−0.06	n.s.	0.19	0.10
T_4 cell count	0.03	n.s.	0.07	n.s.

[a]N does not equal 208 in these analyses.
[b]When the Bonferroni correction for multiple comparisons is used, a per comparison alpha=0.05/16=0.003 should be used to keep the overall alpha at 0.05.

Depression and Level of Hopelessness

Although both depression and level of hopelessness were positively correlated at a statistically significant level, self-ratings of depressive symptoms (depression subscale of the Brief Symptom Inventory) were more strongly related to hopelessness than were clinician ratings (Hamilton depression scale) (table 1). Perhaps this is because the Hamilton scale is intended to distinguish levels of depressive severity in patients diagnosed as having syndromal disorder, and only 14 of the 208 study participants had a current diagnosis of any depressive disorder (major depressive disorder, N=8; dysthymia, N=3; bipolar depression, N=1; and depressive disorder not otherwise specified, N=2). Comparison of scores on the Hopelessness Scale for those men with (N=14) and those without (N=194) current diagnoses of depressive disorders showed a large difference (mean±SD=11.1±6.4 versus 3.8± 3.8; t=3.87, df=203, p=0.002, separate variance estimates).

Physical Status and Level of Hope

As noted, subjects were scored on the presence of current and past (within last 3 months) symptoms and signs commonly but not exclusively associated with HIV infection. The HIV-seropositive subjects had a mean score of 1.7 (range, 0–6); 24 subjects had no symptoms. HIV-seronegative subjects had a mean score of 0.6 (range, 0–4); 47 subjects had no symptoms. Among HIV-positive men, these scores signify the presence, on average, of one or two limited physical symptoms. No relationship was observed for either seropositive or seronegative subjects between HIV symptom score and hopelessness scores. That is, subjects with apparent HIV symptoms, elicited by self-report and physical examination, were no less hopeful than those without any physical symptoms.

In addition to physical symptoms and signs of HIV infection, T cell subsets were assessed. At this baseline evaluation, level of hope was unrelated to T_4 (table 1) or T_8 counts or to T_4-T_8 ratio.

Interaction of Psychiatric Diagnosis, HIV Status, and Hope

We analyzed level of hope in relation to both current psychiatric diagnosis and HIV status. While some of the cell sizes were small, the overall scores showed that, as a group, HIV-positive men had higher Hopelessness Scale scores than did HIV-negative men (mean±SD scores=5.2±4.9 versus 3.2±3.1; t=3.52, df=195, p<0.001); this difference was accounted for largely by the greater hopelessness of men who were both HIV-positive and clinically depressed. These numbers are too small to determine whether this difference is due entirely to the presence of depression or represents an interaction between diagnosis and HIV status.

The question of whether hope is diminished in HIV-positive men in the absence of depressive disorder may be addressed by comparing the mean scores of HIV-positive and HIV-negative men who had no current diagnosis. The difference in their respective mean scores on the Hopelessness Scale (4.2±4.3 versus 2.9±2.6) is statistically significant (t=2.48, df=159, p=0.01) but of doubtful clinical meaning. According to Beck's scale norms, scores of 0 to 3 represent "none to minimal" hopelessness, and scores of 4 to 8 represent "mild" hopelessness. This difference, amounting to one additional item, on average, endorsed by the HIV-positive men, does not appear to justify the conclusion that, as a group, HIV-positive men clearly have lower levels of hope. It is noteworthy, however, that there was a much greater variance and range of scores in the total HIV-positive group, with 24% (N=30) having scores that fell into Beck's classification of moderate or severe hopelessness. In the total HIV-negative group, only eight subjects (10%) scored above 8.

Interaction of Depressive Symptoms, HIV Status, and Hope

The prior analyses were based on the presence or absence of syndromal disorders based on DSM-III-R criteria. We next investigated the relationship of self-reported depressive symptoms present in the past week, as measured by the depression subscale of the Brief Symptom Inventory, to scores on the Hopelessness Scale. In order to assess the relative contributions of HIV status, depressive symptoms, and three other variables with hypothesized relevance to Hopelessness Scale scores, we conducted a hierarchical regression analysis in which we entered HIV status, followed by Brief Symptom Inventory depression subscale scores (from which the hopelessness item was removed), sum of negative life events, social conflict, and the five positive social support subscales combined into a single measure. We did this analysis twice, once for the total sample and again for all subjects without a current depressive disorder.

HIV status contributed only trivially to hopelessness scores (4% of the variance accounted for, including shared variance), while Brief Symptom Inventory depression score was a powerful predictor, accounting for 34% of the variance (25% when subjects with current syndromal depression were removed from the analysis). Negative life events in the past 6 months and level of social conflict contributed no additional variance, while level of social support had a small additional effect (37% of the variance). In a stepwise regression analysis, only HIV status, depression score, and social support score reached tolerance limits needed for entry into the regression equation (HIV status: R=0.21, beta=0.13, T=2.22, p=0.03, df=5, 176, for all analyses; depression score: R=0.58, beta=0.44, T=5.80, p=0.000; and social support score: R=0.62, beta=−0.27, T=−3.51, p=0.001).

In another hierarchical regression analysis, in which HIV status, number of HIV-related symptoms, depression, and social supports were entered in that order, physical symptoms did not add to the variance accounted for beyond the 4% contributed by HIV status. In another analysis in which we used an HIV Status by Depression interaction term, no additional variance was accounted for. Overall, level of hopelessness was not found to be associated with HIV status or presence of HIV symptoms, while depressive symptoms were strongly predictive of hopelessness.

Comparative Levels of Depressive Symptoms

The average score on the seven-item Brief Symptom Inventory depression subscale was lower for seronegative than for seropositive men (mean±SD=1.7±0.7 versus 1.9±0.9; t=2.20, df=188, p=0.03, separate variance estimates). Compared to published norms (20), the scores of both seropositive and seronegative men fell closer to those of normal control subjects (mean=1.3) than to those of psychiatric outpatients

(mean=2.8). Overall, the level of depressive symptoms at this baseline evaluation did not appear to be substantially high for either study group.

DISCUSSION

In our total sample of seropositive and seronegative homosexual men, level of hope was generally high, independent of HIV status. We have replicated the finding of Zich and Temoshok (11) that hope is positively associated with perceived social supports and negatively associated with depressive symptoms. Men with a stronger sense of control over events that they experienced, who had had fewer self-reported depressive symptoms in the past week, who did not have a current diagnosis of depression, and who reported stronger social supports had higher levels of hope. While the zero order correlation between hopelessness score and social conflict was statistically significant, this variable added no additional predictive power after depressive symptoms were entered in a multiple regression analysis, while social supports did make a modest contribution. Evidently, availability of social support contributes more to hope than social conflict detracts.

In this sample, level of hope was not related to number of signs and symptoms commonly associated with HIV infection or to measures of immune status, a finding we plan to pursue in analyses of longitudinal data. It has been suggested (L. Temoshok et al., unpublished data, 1988) that psychological measures may be better predictors of future than concurrent health and immune status, so that perhaps time 1 scores of hopelessness will be associated with time 2 measures of immune status for all subjects or for those few with very high Hopelessness Scale scores at time 1.

While HIV-positive men as a group reported slightly lower levels of hope than did HIV-negative men, this difference was largely accounted for by those with current depressive disorders. Comparison of mean hopelessness scores for HIV-positive and HIV-negative men with no current psychiatric diagnosis showed statistically significant but clinically modest differences, largely accounted for by Brief Symptom Inventory depressive symptom scores. Both groups endorsed an average of three or four items on the 20-item hopelessness scale.

These results are preliminary because of the cross-sectional nature of the data collection, which precludes insight into temporal sequence. Since these results represent the baseline assessment of a 5-year study, with semiannual visits, in the future we will be able to identify antecedents and relationships as they evolve over time.

The research participants in our study were, in general, successful, well-educated men who were motivated enough to volunteer to participate in a study that was not designed to provide any direct benefit. Furthermore, most heard about the study from announcements in newsletters of homosexual organizations, with which they were evidently affiliated. Our sample, then, was a selected group of homosexual men concerned about AIDS. It nevertheless remains noteworthy that despite community decimation and personal vulnerability, they were able to preserve a sense of faith in their future and the conviction that living was still worthwhile.

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The Role of Gender in Studies of Ventricle Enlargement in Schizophrenia: A Predominantly Male Effect

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Two previously reported neuroimaging studies from the authors' laboratory demonstrated larger lateral ventricles in schizophrenic patients than in normal control subjects. This diagnostic effect was accounted for almost entirely by the male subjects. In this report the role of gender is further explored through reexamining these data sets and those of two earlier studies. Although Gender by Diagnosis effects were not demonstrated, in three of the four studies male schizophrenic subjects had significantly larger ventricles than their control counterparts; there were no differences among the female subjects. One study suggested the opposite effect, but this may be attributable to a nonrepresentative control group.
(Am J Psychiatry 1990; 147:1327–1332)

Although schizophrenia is commonly thought of as an illness that affects men and women equally, gender differences have long been recognized, and over the past decade more and more such differences have been reported in the literature. The most consistently reported finding is an earlier age at onset in men (1–4). There is also evidence that female schizophrenic patients respond better to neuroleptics (5, 6) and have a better overall prognosis on a wide variety of outcome measures than do male schizophrenic patients (2, 7, 8). Some studies suggest that there are significant gender differences in symptom expression, with male patients more likely to have a predominantly negative or deficit syndrome and female patients more likely to have affective and paranoid symptoms (3, 9). Such gender differences appear to be more robust when narrower diagnostic criteria such as those of *DSM-III* and *DSM-III-R* are used (10). This type of evidence has prompted some investigators to postulate a two-syndrome model of schizophrenia based on gender: an early-onset, more chronic syndrome primarily affecting men and a later-onset, better-prognosis syndrome predominating in women (11–13).

Significant gender differences in the size and shape of the corpus callosum in schizophrenic subjects have been reported (14), but otherwise gender has not been correlated with morphological abnormalities of the brain in this population. We recently completed two large structural neuroimaging studies of schizophrenic patients (15, 16). The major finding in both studies was the replication of the most consistent finding in all such investigations to date: that the schizophrenic group had a larger mean lateral ventricle size, as measured by the ventricle-brain ratio (VBR), than the control subjects. An intriguing finding in both of these studies was that the group differences were accounted for almost entirely by the male patients. We interpreted these findings cautiously for two reasons. First, among the many structural neuroimaging studies of schizophrenic subjects published to date, gender differences in VBR have not generally been reported (17). Second, there was some duplication of subjects between our studies, which may have accounted for some of the similarity in findings.

We have reviewed the literature, seeking any indication of gender differences with respect to ventricle size in schizophrenia. In the English-language literature, there have thus far been approximately 50 controlled studies of schizophrenia that used computed tomography (CT) and about a dozen that used magnetic resonance imaging (MRI), most of which included a measure of ventricle size. The majority of these reports did not address the gender issue at all; many did not even report the sex ratio of the samples. Sample sizes have typically been small, and male patients have been overrepresented. Table 1 lists the controlled studies of which published reports indicate that there was any analysis of gender with respect to ventricle size. Interestingly, one of the few studies that reported significant sex differences was the largest study.

Takahashi et al. (18) found that male schizophrenic subjects were more likely to have CT scan abnormalities overall and, specifically, that the male subjects had higher rates of abnormality in the left lateral ventricle

TABLE 1. Controlled Studies of Ventricle-Brain Ratio (VBR) That Have Examined Gender Differences in Schizophrenia

Study	Schizophrenic Subjects			Control Subjects			Evidence of Gender Difference in VBR Found in Study
		Sex			Sex		
	Total N	M	F	Total N	M	F	
Takahashi et al., 1981 (18)	270	160	110	234	124	110	M>F
Andreasen et al., in press (15) (CT-2)[a]	80	45	35	63	30	33	M>F
Weinberger et al., 1979 (19)	73	—	—	56	—	—	None
Shelton et al., 1988 (20)	71	49	22	30	14	16	M>F
Iacono et al., 1988 (21)	51	43	8	74	42	32	None
Andreasen et al., 1982 (22) (CT-1)[a]	50	26	24	46	24	22	F>M
Bishop et al., 1983 (23)	47	—	—	25	—	—	None
Andreasen et al., 1990 (16) (MRI-2)[a]	43	29	14	50	29	21	M>F
Williams et al., 1985 (24)	40	30	10	40	28	12	M>F
Smeraldi et al., 1987 (25)	33	28	5	53	34	19	None
Boronow et al., 1985 (26)	30	20	10	26	—	—	None
Reveley et al., 1984 (27)	21	10	11	18	9	9	None
Pearlson et al., 1984 (28)	19	11	8	19	11	8	None

[a]One of the four studies examined in the article.

and third ventricle in addition to decreases in the left and right temporal areas. In another large, more recent study, Shelton et al. (20) found that a comparison of the VBR values of schizophrenic men and women narrowly missed statistical significance ($p < 0.06$), with the men having greater values than the women. The only other study by investigators outside our group that has demonstrated a possible gender effect was done by Williams et al. (24) in 1985, but their results are more difficult to interpret. They noted that among the chronic schizophrenic group, large ventricles were more common in the men than in the women (12 of 21 men versus one of seven women, $p < 0.01$) but that this difference became nonsignificant when the patients were compared to sex-matched control subjects. In terms of MRI studies, the sample sizes have been quite limited, and with the exception of our investigations, none of the reports indicated any analysis of gender with respect to ventricle size.

The purpose of the present work was to investigate this issue further in our data by 1) including VBR data from all available studies of schizophrenia done at our center and 2) eliminating duplication of subjects across studies to see if the pattern would hold. Our hypothesis was that across all studies, male schizophrenic subjects would have larger VBRs than male control subjects and that there would be no difference between the female groups.

METHOD

Four controlled structural neuroimaging studies of schizophrenia have been completed at our center with a total of more than 200 patients and 200 control subjects. We will briefly describe these studies and explain how the data are used in this report.

The first study (22) compared CT findings in a group of 52 schizophrenic patients to those of 47 "medical" control subjects; that is, the control subjects were pa-

tients who had had head CT scans for a variety of nonpsychiatric reasons and whose scans had been read as normal. The schizophrenic group was found to have a larger mean VBR than the control subjects, but gender differences were not analyzed until the present investigation. This study will be referred to as CT-1.

The second study (29) used MRI in samples of 38 schizophrenic and 49 normal control subjects. In this study, which will be referred to as MRI-1, the focus was on cranial and brain size. A midsagittal image was obtained for all subjects, but the coronal and transverse images that are typically used to calculate VBR were obtained only for the patient group because of financial constraints. For the purpose of the present study, those coronal VBR data from schizophrenic subjects were compared to data from the control group in the subsequent MRI study, for which coronal VBR data were available.

The two most recently completed studies were those referred to at the beginning of this article. In the CT study (CT-2) (15), the scans of a sample of 108 schizophrenic patients were compared to those of 75 healthy control subjects. Finally, in the second MRI investigation (MRI-2) (16), coronal, sagittal, and transverse images of 55 schizophrenic subjects were compared to those of 47 normal control subjects.

The demographic and clinical data, as well as the scanning and measurement methodology, have been described in detail in the individual reports. The sampling methods for the patient groups were identical in all four studies. That is, the schizophrenic subjects were drawn from consecutively admitted hospital patients whose primary diagnosis according to *DSM-III* criteria was schizophrenia; they had no evidence of mental retardation, history of head trauma leading to loss of consciousness, or any other neurological or serious medical illness. There were no significant differences across the four patient samples on any sociodemographic or clinical measure. As we have noted, control subjects for the CT-1 study were selected by

searching the files of the radiology department for medical patients who had been found to have normal head CT scans. Control subjects for the subsequent studies were healthy volunteers who had been recruited from the community to be equivalent to the patient groups in terms of age, gender, socioeconomic status, and education. All subjects gave written informed consent for participation in the studies. For both CT studies, an area VBR was determined by mechanical planimetry after raters blind to the diagnosis traced the outline of the ventricles and the inner table of the skull in the slice in which the lateral ventricles were seen at their largest. The earlier CT study used scanners that provided a 160×160 matrix, whereas the more recent study used a 256×256 pixel matrix. Both MRI studies were done on a Picker 0.5-Tesla scanner, and for both studies the coronal cuts used for obtaining the VBR were done with the same inversion recovery sequence (inversion time=600 msec and repetition time=1600 msec). For these studies a volumetric rather than an area VBR was calculated. That is, the area data from consecutive slices were obtained by using the same procedure as in the CT studies; they were then summed for an estimation of volume.

Of a total of 213 schizophrenic patients, 34 participated in multiple studies. Among these patients, 23 participated in one CT and one MRI study, one was in both CT studies, eight were in three studies, and two participated in all four studies. Excluding the control subjects who were in the MRI-1 study (because VBR data could not be accurately determined), of the 162 remaining control subjects, 12 participated in both the CT-2 and the MRI-2 studies, but there was no other duplication. For this analysis we chose to assign the subjects who participated in multiple studies to the study with the smallest number in each group. From the largest to the smallest, the order was CT-2, MRI-2, CT-1, and MRI-1 for patients and CT-2, MRI-2, and CT-1 for control subjects.

RESULTS

The cell sizes and VBR means and standard deviations for each subject group (after duplication of subjects was eliminated) are presented in table 2. After establishing the nonduplicate groups, we performed four Gender by Diagnosis analyses of variance (ANOVAs), one for each study. Of particular interest to us was the Gender by Diagnosis interaction. We hypothesized that this would be significant and indicate a significantly larger diagnostic effect for male subjects than for female subjects. Since this was an a priori hypothesis, we conducted tests of simple main effects, specifically, diagnostic effects within each gender. Also, gender effects for the patients and control subjects were investigated.

The ANOVA results are shown in table 3. Since the MRI-2 control sample was used for comparison with the schizophrenic sample in MRI-1, these two analyses

TABLE 2. Ventricle-Brain Ratios (VBRs) of Schizophrenic and Control Subjects by Gender in Four Studies[a]

Study and Group	Male Subjects VBR[b] N	Mean	SD	Female Subjects VBR[b] N	Mean	SD
CT-1 (22)						
Schizophrenic subjects	26	6.34	4.75	24	5.81	2.95
Control subjects	24	5.05	3.20	22	3.67	2.75
CT-2 (15)						
Schizophrenic subjects	45	7.11	3.45	35	6.35	2.29
Control subjects	30	5.20	2.57	33	6.18	2.62
MRI-1 (29)						
Schizophrenic subjects	25	2.26	0.57	10	2.14	0.51
Control subjects[c]	29	1.78	0.65	21	2.01	0.88
MRI-2 (16)						
Schizophrenic subjects	29	2.49	1.00	14	2.15	0.98
Control subjects	29	1.78	0.65	21	2.01	0.88

[a]Table reflects data sets that were established after subjects who had participated in multiple studies were assigned to only one.
[b]VBR values from CT and MRI studies are not directly comparable, since CT values are ratios of *area* measurements in one slice, whereas MRI values are derived from ratios of ventricular and cerebral *volumes* throughout the brain.
[c]The control sample shown for MRI-1 is a duplication of the sample used for MRI-2.

TABLE 3. Gender by Diagnosis Analysis of Variance on Ventricle-Brain Ratios in Four Studies

Study	F Value Gender	Diagnosis	Gender by Diagnosis	df
CT-1 (22)	1.92	5.62[a]	0.34	1, 92
CT-2 (15)	0.06	4.71[a]	3.29	1, 139
MRI-1 (29)	0.11	3.62	1.10	1, 81
MRI-2 (16)	0.11	5.02[a]	2.23	1, 92

[a]$p < 0.05$.

are not independent. Replicating previous findings of larger ventricles in schizophrenic patients, all but one study showed a significant diagnosis effect. Had these been one-tailed tests, all results would have been significant. There were no indications of an overall gender effect in any of the analyses.

Contrary to our hypothesis, none of the interactions proved significant. The CT-2 study had yielded a significant Gender by Diagnosis effect when the full sample was analyzed, but the interaction did not reach significance (F=3.29, df=1, 139, p<0.07) when we reduced the sample size by approximately 75% due to duplication of subjects. Because of our a priori hypothesis, we proceeded with the tests of simple main effects in spite of the nonsignificant interactions. The results of these tests are shown in table 4. These were t tests based on the mean difference of two subgroups, specifically, a comparison of two means of one factor (e.g., diagnosis) separately for each level of the other

TABLE 4. Simple Main Effects of Gender and Diagnosis on Ventricle-Brain Ratio In Four Studies

	t Value				
	Diagnosis[a]		Gender[b]		
Study	Male Subjects	Female Subjects	Control Subjects	Schizo-phrenic Subjects	df
CT-1 (22)	1.29	−2.05[c]	1.31	0.52	92
CT-2 (15)	−2.86[d]	−0.25	−1.38	1.18	139
MRI-1 (29)	−2.55[d]	−0.52	−1.13	0.45	81
MRI-2 (16)	−3.08[d]	−0.47	−0.88	1.21	92

[a]Differences between genders within diagnoses.
[b]Differences between diagnoses within genders.
[c]$p<0.05$.
[d]$p<0.01$.

factor (e.g., gender). For instance, in the MRI-2 sample, the difference between the two diagnostic groups for male subjects was significant ($t=-3.08$, $df=92$, $p<0.01$), while for female subjects it was nonsignificant ($t=-0.47$, $df=92$, $p>0.50$). We present tests based on estimates of parameters in full general linear model, rather than conventional tests of simple main effects, in order to deal with the unbalanced cell sizes.

As indicated in the initial ANOVAs, table 4 shows no overall gender effects in the control subjects or the schizophrenic patients. All studies showed a diagnosis effect for one gender but not the other. In support of our original hypothesis—that the main effect for diagnosis would be mostly due to the effect in male subjects—three of the four studies showed clear differences for male but not for female subjects. Interestingly, the other study, CT-1, showed just the opposite effect.

DISCUSSION

Although we will refer to gender differences in this discussion, it is important to emphasize that we did not find any simple differences in VBR between male and female schizophrenic patients or between male and female control subjects. We did find that in all but the CT-1 data set, male schizophrenic subjects had significantly larger VBRs than did male control subjects, whereas the female schizophrenic subjects did not differ from the female control subjects. While the CT-1 analysis yielded seemingly opposite results (i.e., greater differences between the female than the male groups), a closer look at the data shows that the findings of the CT-1 study were not entirely inconsistent with those of the other studies. As illustrated in table 5, all four studies demonstrated that the mean VBR of the male schizophrenic patients was substantially larger than that of the male control subjects and slightly larger than that of the female schizophrenic patients. The anomalous group appears to be the female control sample in CT-1, whose mean VBR was significantly different from that of the CT-2 female control sample

TABLE 5. Ratios of Ventricle-Brain Ratio (VBR) Means From Each Cell in Four Studies[a]

Study	Male Control/ Male Schizo-phrenic Subjects	Female Control/ Female Schizo-phrenic Subjects	Female Schizo-phrenic/ Male Schizo-phrenic Subjects	Female Control/ Male Control Subjects
CT-1 (22)	0.80	0.63	0.92	0.73
CT-2 (15)	0.73	0.97	0.89	1.19
MRI-1 (29)	0.79	0.94	0.94	—
MRI-2 (16)	0.72	0.93	0.93	1.13

[a]Ratios are derived from the mean VBR values presented in table 2.

($t=3.42$, $df=53$, $p<0.01$). These findings, along with the methodological differences in CT-1 ("medical" rather than normal control subjects and older scanning equipment), lead us to weight the CT-1 study less heavily in our interpretation of the data. It is, however, important to note that in the two subsequent control samples, the female subjects had nonsignificantly larger VBRs than the male control subjects. Although none of the studies we reviewed revealed significant gender differences among the control subjects, if any differences did exist, they tended to be in the direction of larger VBRs among the male subjects. We were therefore concerned that the gender effect observed in the original CT-2 and MRI-2 samples might have been a consequence of an anomalous patient or control sample. The results of the reanalysis presented here demonstrate that the MRI-2 study indeed replicated the CT-2 findings, with two independently recruited samples of normal volunteers and no duplication of subjects across studies. The analysis of the MRI-1 patient sample adds further support to the conclusion that ventriculomegaly among schizophrenic subjects is a predominantly male effect.

Our review of the literature was remarkable for the fact that three of the four largest controlled studies suggested a predominance of ventricle enlargement among male schizophrenic patients, whereas gender differences were not demonstrated in most of the smaller studies. This finding, taken together with our findings of nonsignificant Gender by Diagnosis interactions, indicates that if a gender effect does exist, it is subtle, and studies with adequate power to detect such an effect will probably require sample sizes at least as large as those of the larger studies listed in table 1.

If small sample sizes have obscured real but subtle and complex gender differences with respect to greater VBR in schizophrenia, what is the practical significance of this finding? While the implications remain unclear, any observed gender differences in clinical or biological variables can be exploited in the etiological investigation of the illness, particularly in the effort to tease apart the contributions of genetic and environmental factors. Higher rates of obstetrical complications (30) and head trauma (31) have been recognized in schizophrenic patients, implicating environmental

factors in the etiology. Increased VBR may be a marker for a prominent environmental component, as there appears to be an inverse relationship between family history and ventricle enlargement in schizophrenia (27), as well as an association between perinatal complications and enlarged ventricles both in normal subjects (27) and in schizophrenic subjects (32). Cannon et al. (33) recently demonstrated that a combination of genetic and environmental factors may result in ventricle enlargement, as increased ventricle size appears to correlate with obstetrical complications in subjects who are at high genetic risk for schizophrenia. In a review of the Iowa 500 data, Nasrallah and Wilcox (34) found that among schizophrenic subjects, men were significantly more likely than women to have the combination of brain injury (broadly defined) and no family history of psychosis, and women were more likely to have the reverse pattern. Males are at higher risk for a variety of developmental disorders, notably those primarily involving the left hemisphere, such as dyslexia, stuttering, and autism (35). This may have relevance to schizophrenia, as there is some evidence of specific left-sided pathology in neuropathological and imaging studies in this disorder (36, 37). Given all of these considerations, the hypothesis that male schizophrenic patients are more likely to have enlarged ventricles than female patients is theoretically appealing; it is consistent with a model in which ventriculomegaly is a nonspecific marker of a developmental and/or perinatal abnormality associated with schizophrenia, to which males are more vulnerable than females.

As we noted earlier, male schizophrenic patients have been found to have greater chronicity, poorer response to neuroleptics, poorer overall outcome, and more prominent negative symptoms than female patients with the illness. In light of the findings presented here, it is interesting to note that these four clinical variables are among the six initially presented by Crow (38) in characterizing the type II or negative syndrome. Our findings suggest that yet another type II variable— that is, cell loss/structural brain abnormalities—may be more common in male patients. The hypothesis that men are more likely than women to have the type II pattern may be worth testing.

Finally, since enlarged ventricles are not specific to schizophrenia (39), it may be worth investigating such a gender effect in other psychiatric disorders in which this structural abnormality is observed. Our own work (40) suggests that there may be such an effect in bipolar disorder.

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Socioeconomic Status, Ethnicity, Psychological Distress, and Readiness to Utilize a Mental Health Facility

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The effects of minority status versus ethnic culture on Mexican-Americans' underutilization of mental health services were reassessed through development and testing of an analytic path model that proposes a sequence of factors, including Mexican-American ethnicity, socioeconomic status, degree of social and institutional support, and depression, which culminate in a person's decision to utilize mental health facilities. The model also predicts that life stress will affect utilization through its influence on depression. Data from 783 subjects generally supported the model's predictions. A multifactorial approach to the causes of mental health problems and utilization behavior in the Mexican-American population is suggested.

(Am J Psychiatry 1990; 147:1333–1340)

The clinical literature shows that various ethnic and socioeconomic groups differ widely in their utilization of and attitudes toward professional mental health services (1, 2). Findings over a 20-year period (3–8) showed that persons of lower socioeconomic status tend not to utilize professional services of any kind except in extreme situations.

A recurring assumption is that underutilization represents one manifestation of the "general estrangement of the poor from mainstream middle-class society and its social institutions" (9, p. 301). Strauss (10), for example, noted that poverty per se creates its own lifelong ambiguous existence. Similarly, Gans (11) noted that coping with poverty necessitates a highly personalized world view quite antithetical to that needed for coping with health care bureaucracies. Bureaucratic

systems are in fact "the key medium through which the middle class maintains its advantaged position vis-à-vis the lower class" (12, pp. 395–396).

Hoppe and Heller (9), in their review of studies concerning the poor, noted that lower-class populations across nations possess a number of similar characteristics. These include a distrust of the world outside family and friends, a perception of the world in general as chaotic and catastrophic, heavy involvement in familial and peer relationships, and lack of community participation.

Like underclass populations in general, Mexicans and Mexican-Americans are said to perceive the world outside family and friends in fatalistic terms. Along with patriarchy and familism, this fatalistic belief system is seen by some to be rooted in the Mexican heritage (13) or culture (14–17) and by others to be rooted in socioeconomic conditions associated with poverty (18–20). There have been underutilization studies specifically comparing Mexican-Americans and Anglo-Americans (21), and findings of underutilization of mental health services by Mexican-Americans have been reported and "interpreted" by Edgerton et al. (22) and Karno and Edgerton (23, 24). These authors explained Mexican-American underutilization in terms of folk beliefs and illnesses. Another study (25) suggested that acculturation to Anglo society constituted a positive influence on help-seeking behavior among Mexican-Americans residing in Los Angeles. The current debate on underutilization appears to focus on what Mirowsky and Ross (26) referred to as the minority status versus ethnic culture perspective. The former view contends that when a minority group is in a disadvantaged position, associated stressors will produce greater socioeconomic and psychological distress. The latter perspective maintains that socioeconomic and psychological well-being are associated with cultural attributes such as beliefs, values, and lifestyle (27).

We argue that the debate on the structural versus the cultural view begs the question. Clearly, the decision to seek professional mental health care is influenced by many factors, including one's ethnicity and socioeconomic status. We readdress this issue in terms

FIGURE 1. Theoretical Path Model for Variables Relating to Readiness to Utilize Professional Mental Health Care[a]
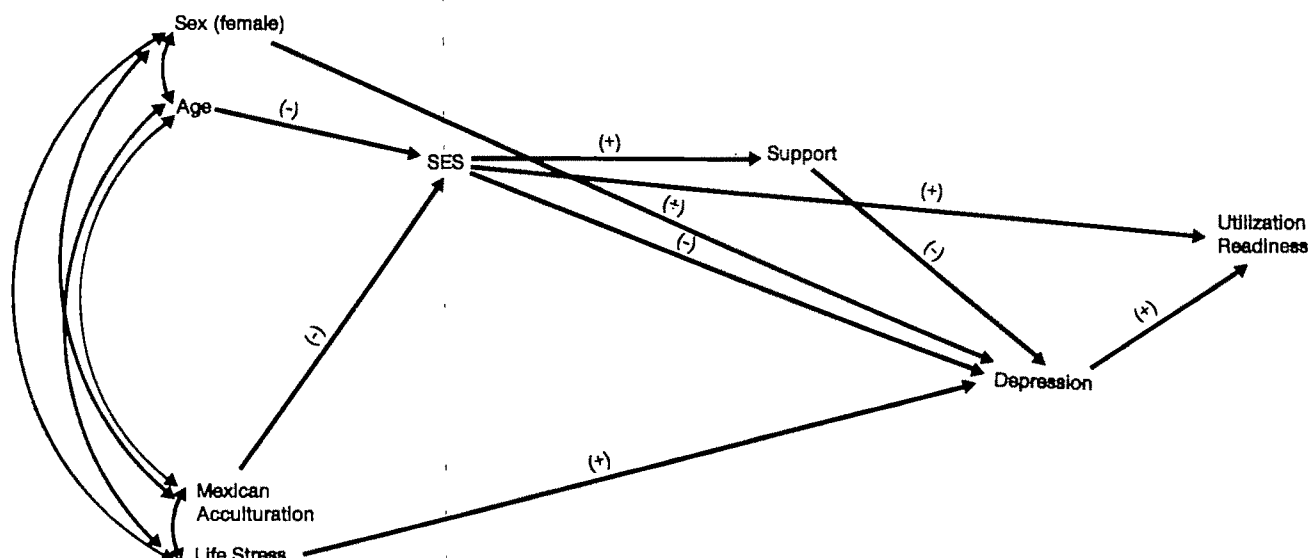
[a]SES=socioeconomic status.

of a hypothesized sequence of factors that culminate in one's attitude toward utilization of mental health facilities.

THE HYPOTHESIZED MODEL

Our model (see figure 1) asserts that certain variables independently and in combination influence a person's readiness to seek professional help. We suggest that conditions associated with low socioeconomic status exacerbate the effects of alienation faced by Mexican-American populations. Conversely, relatively high socioeconomic status mitigates many of the consequences of this alienation. Thus, Mexican-American ethnicity and low socioeconomic status combine to directly inhibit participation in the bureaucratic system of mental health care.

These factors alone, however, provide only a partial explanation for mental health care utilization. Readiness to seek professional mental health care develops from a combination of physical, socioeconomic, and psychological conditions. The effects of sex, age, and ethnicity on one's readiness to use professional services are influenced by such factors as socioeconomic status, stressful life events (28–30), and inclusion within a social support network (31, 32). These events, in turn, affect the amount of psychological distress (in our model, depression) exhibited by any given individual.

Socioeconomic status is the pivotal link between ethnicity, social support, and depression. Persons of high socioeconomic status tend to have institutional and social support systems that insulate them from depression. Individuals of high socioeconomic status are often comfortable with community associations and

agencies, including the community's mental health care delivery system. It is agreed that Mexican-Americans with strong support networks will have relatively low levels of depression. However, this is also predicted for Anglo-Americans. Thus, it is minority status in interaction with low socioeconomic status that leads to a lack of social and institutional support and a higher degree of depression. Regardless of ethnicity, persons of relatively high socioeconomic status are expected to utilize professional mental health care services when needed; thus, socioeconomic status is predicted to have a direct effect on readiness for utilization. However, socioeconomic status is expected to affect degree of social and institutional support and degree of depression even more strongly than readiness for utilization. Like ethnicity, socioeconomic status is better seen as an indirect determinant of readiness to seek professional care.

As in the case of ethnicity, the model predicts that the effects of sex and age on readiness for utilization will be indirect. It predicts that women will manifest a relatively high degree of depression, thus favoring their readiness to seek professional help. Age is predicted to have an indirect effect on readiness for utilization through socioeconomic status, as elderly persons are predicted to have less education and less income than younger people. Age is not predicted to affect either support or depression directly.

Stressful life events can assail an individual—regardless of gender, age, ethnicity, socioeconomic status, or the presence of a support network—and induce psychological distress. For this reason, the model predicts that life stress forms an indirect path through depression to readiness for utilization of mental health services.

METHOD

A stratified random sample of 806 respondents residing in the El Paso Standard Metropolitan Statistical Area was selected and interviewed in 1985 and 1986. Six census tracts representing upper-middle-class, middle-class, and lower-class areas for Anglos and Hispanics were selected. In all, 783 of the 806 respondents could be classified without ambiguity as Mexican or Mexican-American (N=446) or Anglo-American (N=337). Data on the 23 nonclassifiable respondents were excluded from the analysis.

Data were collected during face-to-face interviews. The interview schedule was originally written in English and subsequently translated into Spanish. It was administered in Spanish or English, depending on the respondent's preference. Bilingual interviewers were trained to respond appropriately to clinically oriented requests by the respondents, and the importance of cultural sensitivity (33) was stressed during the interviewers' training.

The model's dependent variable, readiness for self-referral (utilization readiness), was measured with a slight modification of a series of questions developed by Kulka et al. (8). These questions—the exact wording has been published elsewhere (34)—pertained to actual and potential utilization of mental health care resources for broadly defined personal problems. Responses to these questions were categorized and numerically coded as 1) strong self-help orientation (could always handle things without help), 2) mild utilization readiness (could possibly have a problem with which a professional source might help), 3) moderate utilization readiness (had a problem with which a professional source might have helped, and 4) strong utilization readiness (received help for a personal problem). The numbers of respondents classified into these response categories were 241, 182, 89, and 263, respectively. Responses to these questions were not ascertained for eight of the 783 respondents.

In addition to utilization readiness, four exogenous and three endogenous variables are included in the model. (An exogenous variable is here defined as a variable determined by others lying outside the causal model. The term "endogenous variable" refers to that which is determined by the model's exogenous variables or by an antecedent endogenous variable.) The exogenous variables are sex (female=1, male=0), age (coded as given), ethnicity, and life stress. In agreement with a number of authors (13, 35, 36), Hispanic ethnicity is considered to be a continuous rather than a discrete variable. Ethnicity is thus defined as the respondent's degree of Mexican acculturation. A Mexican acculturation scale was constructed from factor-analyzed items developed by Cuellar et al. (37). Scale items measure the degree to which certain activities and events, such as Mexican songs, fiestas, culture, and sports, are important. Scale items (multiplied by their factor loadings) are summed. Cronbach's alpha for this scale is 0.96.

Life stress was measured by 23 questions about health-related and non-health-related stressful life events developed by Thoits (38). Respondents were asked whether any of these events had occurred within a period of approximately 1 year before the interview. Events were summed to give the respondent's life stress score (38, p. 102).

The model's three endogenous variables include socioeconomic status, support, and depressive symptoms. Socioeconomic status was measured by the respondent's degree of formal education and yearly family income. Before education and income were combined into one socioeconomic status scale, z scores were computed for each.

Social and institutional support items were highly correlated among these respondents. Due to problems of collinearity, these items were combined into a general support measure after z scores had been computed for each variable. Respondents were read five statements dealing with loss of income and hospitalization of a spouse over a period of several weeks. The statements dealt with the extent to which the respondent would have familial, friends', and/or institutional support during such stressful periods. Responses to these statements were numerically coded as 1 ("This statement in no way fits my life today"), 2 ("This statement somewhat fits my life today"), or 3 ("This statement strongly fits my life today"). Responses to these five statements were summed to form a general support score for each respondent.

Depression was measured by the 22-item Center for Epidemiologic Studies Depression Scale (CES-D Scale) developed at the National Institute of Mental Health. The scale has been well tested (39) and extensively used for both Anglo and Mexican-American populations (40). Cronbach's alpha for this scale is 0.92.

The path analysis performed in this study was identical to that elucidated by Kerlinger and Pedhazur (41, pp. 305–333). We began the data analysis by regressing each lower-level variable against all higher-level variables. Thus, socioeconomic status was regressed against sex, age, Mexican acculturation, and life stress; support was regressed against sex, age, Mexican acculturation, life stress, and socioeconomic status; depression was regressed against sex, age, Mexican acculturation, life stress, socioeconomic status, and support; and utilization readiness was regressed against sex, age, Mexican acculturation, life stress, socioeconomic status, support, and depression. The model was then trimmed (41, p. 318) by eliminating from each equation any variable with a standardized coefficient less than 0.100 and a t test probability level greater than 0.001 (one-tailed test). The clinical implications of this research required that meaningfulness of findings outweigh statistical significance (41, p. 318) as the criterion for deletion of inconsequential paths. For this reason the customary (41, p. 318) minimum standardized coefficient and the statistical probability level of 0.05 were rejected in favor of those we have mentioned. After deleting nonmeaningful variables

FIGURE 2. Empirical Path Model (Standardized Coefficients) for Variables Relating to Readiness of 783 Subjects to Utilize Professional Mental Health Care[a]
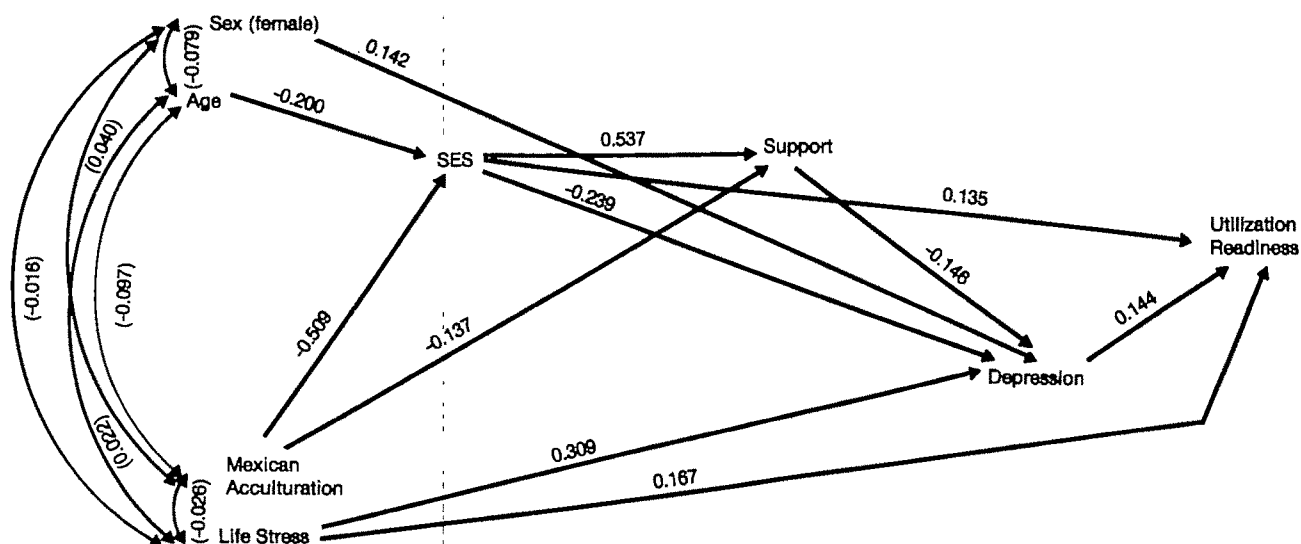
[a]SES=socioeconomic status. Numbers in parentheses are zero-order correlations.

TABLE 1. Regression Results (Unstandardized Coefficients) in the Empirical Path Model for Variables Relating to Readiness of 783 Subjects to Utilize Professional Mental Health Care

Variable	Socioeconomic Status		Social and Institutional Support		Depression		Utilization Readiness	
	Coefficient	SE	Coefficient	SE	Coefficient	SE	Coefficient	SE
Sex (female)	—	—	—	—	2.957	0.654	—	—
Age	−0.020	0.003	—	—	—	—	—	—
Mexican acculturation	−0.114	0.007	−0.031	0.007	—	—	—	—
Life stress	—	—	—	—	1.395	0.161	0.104	0.023
Socioeconomic status	—	—	0.543	0.033	−1.395	0.229	0.096	0.026
Social and institutional support	—	—	—	—	−0.843	0.228	—	—
Depression	—	—	—	—	—	—	0.017	0.005
Intercept	2.942		0.542		23.244		1.769	
R²	0.279		0.379		0.247		0.069	

from each multiple regression equation, we repeated the path analysis. The final empirical model (see figure 2) was then interpreted in terms of its confirmation or lack of confirmation of the hypothesized model (figure 1).

RESULTS

Results of the data analysis are presented in table 1 and in figure 2. Included in table 1 are regression results for the empirical path model, with unstandardized regression coefficients, the standard error of each unstandardized regression coefficient, and the multiple correlation squared of each multiple regression equation. Figure 2 depicts the empirical model, presenting paths where standardized regression coefficients were greater than 0.100.

Results in Support of the Model

Figure 1 predicts a path sequence linking the presence of a support network to utilization readiness through depression. Specifically, support is predicted to have a negative effect on depression, which in turn is expected to have a positive influence on utilization readiness. The empirical path model confirmed this predicted path sequence. Figure 2 shows that support had a significant standardized negative effect on depression after we controlled for the effects of sex, socioeconomic status, and life stress. The higher the degree of social and institutional support, the less depression was experienced. Depression, in turn, had a significant positive standardized effect on utilization readiness. Since support did not form a direct path to utilization readiness, depression represents a key to this phenomenon.

Figure 1 also predicts that the effects of socioeconomic status on utilization readiness will follow three path sequences. One predicted path links socioeconomic status to utilization readiness through depression. The findings presented in figure 2 uphold this contention. A second anticipated path links depression to socioeconomic status through support. This prediction was also fulfilled. Socioeconomic status had a positive and sizable standardized effect on support, and support was also significantly but negatively associated with depression. Thus, higher socioeconomic standing favored a tendency to have meaningful support, which in turn decreased the probability of depressive symptoms.

Figure 1 also predicts a direct path linking socioeconomic status and utilization readiness. However, the standardized regression coefficient for this path was expected to be distinctly smaller than those linking socioeconomic status with both support and depression. This prediction was also upheld. Socioeconomic status induced a significant but relatively small positive direct effect on utilization readiness. The corresponding standardized regression coefficients for the socioeconomic status-depression and socioeconomic status-support paths were considerably larger. Thus, as predicted, a path between socioeconomic status and utilization readiness is better understood in terms of indirect linkages through either support or depression.

As previously noted, socioeconomic status represented the key variable in linking ethnicity to support, depression, and/or utilization readiness. Mexican acculturation (ethnicity) was predicted to form a direct path only to socioeconomic status. As predicted, Mexican acculturation induced a strong standardized direct effect on socioeconomic status. Indeed, the standardized regression coefficients for Mexican acculturation-socioeconomic status and socioeconomic status-support represented the strongest findings shown in figure 2. The indirect path between Mexican acculturation and depression via socioeconomic status was also represented by sizable regression coefficients. Thus, socioeconomic status represents the pivotal link between Mexican acculturation and depression.

In our model life stress is unrelated to either ethnicity or socioeconomic status. As predicted, life stress directly affected depression (figure 2). Thus, life stress had a sizable influence on depression, which in turn affected utilization readiness.

Finally, the model predicts that the respondents' sex and age will indirectly affect utilization readiness by directly influencing depression and socioeconomic status, respectively. Figure 2 shows that the path from sex to utilization readiness runs through depression. Thus, as predicted, the women were more likely than the men to report depressive symptoms. The effects of the respondents' age on utilization readiness were also indirect. Age induced a standardized direct effect on socioeconomic status.

Anomalous Results

Two anomalous findings are depicted in figure 2. The theoretical model (figure 1) predicts that ethnicity will influence utilization readiness only through two path sequences: from ethnicity through socioeconomic status to support and from ethnicity through socioeconomic status to depression. Socioeconomic status, in fact, is viewed as the key link among ethnicity, support, and depression. Figure 2 shows that evidence for these predictions was somewhat ambiguous. Clearly in line with our prediction, the strongest effects of ethnicity on utilization readiness and depression ran through socioeconomic status and support. Indeed, ethnicity induced a sizable standardized direct effect on socioeconomic status. Contrary to our expectation, however, Mexican acculturation also had a significant and negative standardized direct effect on support. Thus, an unpredicted sequence appears to bypass socioeconomic status and run from ethnicity to utilization readiness through support and depression. Despite this unexpected finding, it is clear that ethnicity directly affected neither utilization readiness nor depression. As predicted, ethnicity worked in conjunction with socioeconomic status either to directly affect a person's tendency toward depression (and, therefore, utilization readiness) or to influence these phenomena indirectly through affecting the person's ability to form meaningful social and institutional support networks. Nevertheless, even after we controlled for the effects of socioeconomic status, the Anglo-Americans were more likely than the Mexican-Americans to have social and institutional support networks that might insulate them against depression.

The second anomalous finding concerns the life stress variable. In figure 1, life stress is predicted to bypass all variables in the model except depression in affecting utilization readiness. It is also anticipated that life stress and depression will form a path sequence ending in utilization readiness. Figure 2, however, shows that life stress independently affected utilization readiness. Nevertheless, the major explanatory power of life stress in predicting utilization readiness was channeled through depression, and the standardized effect of depression on utilization readiness was only somewhat less than the effect of life stress on utilization readiness. Thus, life stress had a sizable influence on depression, which in turn affected utilization readiness.

In summary, findings presented in figure 2 generally confirm our original model (figure 1). Two anomalous findings include direct effects of ethnicity on support when socioeconomic status was controlled and direct effects of life stress on utilization readiness when depression and socioeconomic status were controlled. With respect to the first anomaly, socioeconomic status was clearly the most important contributor to support. After we controlled for ethnicity, socioeconomic status induced a sizable standardized direct effect on

support, whereas the standardized direct effect of ethnicity on support was significant but much smaller. Thus, the hypothesized sequence among ethnicity, socioeconomic status, and support was clearly upheld.

The same pattern occurred for the second anomalous finding. The standardized direct effect of life stress on depression was clearly more meaningful than that of life stress on utilization readiness. Thus, the hypothesized path for life stress to utilization readiness through depression received confirmation.

Most importantly, these findings uphold our contention that ethnicity and socioeconomic status are best viewed as part of a multiplicity of factors leading to a decision to seek help during periods of emotional crisis. Specifically, ethnicity and socioeconomic status indirectly affect this decision by influencing such factors as having a support network and the tendency to become depressed. Nevertheless, socioeconomic status alone and life stress alone are virtually as powerful predictors of utilization readiness as is depression.

DISCUSSION

We offer the path model presented in this article as an alternative to what has become a sterile debate on minority status versus ethnic culture. This model represents an attempt to integrate a number of variables that have been found in past research to affect utilization behavior. Rather than focusing on the individual and collective effects of seven variables, we sought to develop and test a causal model of projected paths through which one variable influences another. These path sequences culminate in a person's decision to utilize professional mental health care when confronted with an emotional problem.

The model's predicted path sequences were empirically confirmed. Membership within the Anglo category was associated with higher socioeconomic status, which in turn was associated with having a support network capable of safeguarding the individual against depression. The latter finding was so pronounced that (contrary to our prediction) a direct path led from Anglo ethnicity to support when we controlled for socioeconomic status.

Especially interesting is the lack of a meaningful path between ethnicity and the tendency toward depression. Even with the frequent prejudice and discrimination faced by Mexican-Americans—rich and poor alike—Hispanic origin alone did not meaningfully affect predisposition to depression. This same pattern existed for utilization readiness. The literature on this subject is replete with arguments that America's health care delivery system is run by and for well-to-do Anglos. Nevertheless, it was class position, rather than ethnicity, that provided a direct path to utilization readiness. This result corresponds to findings from a study (42) of board membership lists from community mental health service agencies in San An-

tonio, Tex. Although a high proportion of board members had Spanish surnames, virtually all of these persons lived in high-income census tracts. Thus, it appears that high socioeconomic status mitigates many of the effects of minority status by placing persons in a prestigious and affluent network of relationships and memberships.

As predicted, life stress affected utilization readiness through depression. Life stress, however, also directly affected utilization readiness and was therefore an important variable in explaining both depression and utilization readiness. Of all the paths leading directly to depression, life stress had the strongest standardized effect (see figure 2). The same finding held true with respect to utilization readiness. Thus, knowledge of a person's life stress is of considerable value to those interested in predicting the onset of depression. Life stress is also an important motivating factor in a person's decision to seek help.

Finally, possession of a meaningful support network constitutes a pivotal link between ethnicity and socioeconomic status and the presence of depressive symptoms. Thus, the alienating effects of minority status and lower-class existence are buffered by having a meaningful support network. Persons in these circumstances may be shielded from depression and be less likely to need professional mental health care when faced with a multitude of problems.

This study indicates that clinicians need to assume a multifactorial approach in envisioning the causes of mental health problems in the Mexican-American population. In demonstrating how multiple variables merge to produce clinical problems, we have attempted to show how these same variables interact in affecting decisions to approach (or avoid) professional mental health services. Clinicians have noted that Mexican-American patients' difficulty in approaching institutional caretakers arises from problems in perceiving any possible benefits from their services as well as a frank mistrust of the clinical setting (43). The results of our study indicate multiple reasons for the formation of resistances that lead to nonutilization of mental health services and refute arguments that emphasize a single dominant factor (such as ethnicity).

While some types of psychopathology appear to have primary biological mechanisms, sociocultural factors can exert a powerful impact on the expression of the final psychopathological state. We support a theoretical orientation that conceptualizes many psychiatric symptoms as the expression of a complex interplay of human systems at the macrosocial, microsocial, psychosocial, biobehavioral, and biopsychological levels (44). Given this model, our study attempted to demonstrate the impact of variables defined as macrosocial (acculturation), microsocial (support network), psychosocial (life stress), and biobehavioral (depression). We feel that the path model can readily lend itself to the analysis of multiple, clinically relevant variables within such hierarchical systems.

The setting for this study, El Paso, Tex., is a border community with large populations of Mexican-Americans and Anglo-Americans. The demographic characteristics of the area, including the dynamic migrant patterns, provide a fertile ground for the study of the dynamics of acculturation and its impact on the clinically relevant variables we have addressed. In agreement with Yamamoto and Silva (21), we feel that further research in this area should be longitudinal in nature and should compare border with nonborder populations. This approach would be invaluable for understanding how hierarchical variable systems interact in producing psychopathology within and across ethnic groups. Findings concerning Hispanic populations may or may not be relevant to other ethnic groups. The pioneering work of Parker and Kleiner (45)—in which the methodology was not directly comparable to ours—suggested that socioeconomic status is not a relevant variable in explaining psychological distress among African-Americans. Thus, future theoretical models should integrate macro-level variables and biopsychosocial systems (cellular and neurochemical factors) and be tested simultaneously on more than one ethnic group.

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New Policy of Structured Abstracts

Effective with the January 1991 issue, *The American Journal of Psychiatry* will institute a policy of structured abstracts for Special Articles and Regular Articles. Authors of Special Articles must include the following key information: purpose (the primary objective of the review article); data sources (a brief summary of sources); study selection (the number of studies selected for review and how they were selected); data extraction (rules for abstracting data and how they were applied); results of data synthesis (the methods of data synthesis and key results); and key conclusions, including potential applications and research needs. Authors of Regular Articles must include in the abstract the following key information: objective (the questions addressed by the study); design of the study; setting (location and level of clinical care); patients or participants (the manner of selection and number who entered and completed the study); interventions (the exact treatment or intervention, if any); main outcome measures (the primary study outcome measure as planned before data collection began); results (key findings); and key conclusions, including direct clinical applications. Also effective with the January 1991 issue, abstracts for Special Articles and Regular Articles will be increased to a maximum of 250 words and the abstracts for Clinical and Research Reports will be increased to 60 words.

Effect of Time-Limited Psychotherapy on Patient Dropout Rates

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The authors conducted an archival study of 149 new clinic patients at a large community mental health center. The dropout rate for patients in brief psychotherapy in which the length of therapy was specified at the outset of treatment (time-limited psychotherapy) (32%) was about one-half the dropout rate for patients in brief (67%) and long-term (61%) individual psychotherapy. The difference in dropout rates could not be explained by patient demographic or diagnostic variables or by therapist characteristics measured in the study. The results suggest that setting a specific time limit on individual psychotherapy at the outset of treatment can reduce the patient dropout rate in a public mental health clinic.

(Am J Psychiatry 1990; 147:1341–1347)

Dropping out of psychotherapy is a common clinical phenomenon (1–4). A 1986 review of research (2) indicated that more than 50% of outpatients withdraw before the eighth session. The dropout phenomenon is generally believed to be a function of patient variables, environmental circumstances (e.g., influences of family, work, and friends), therapeutic setting, therapist characteristics, and the interaction between therapist and patient (1–3). Whatever the causes of a patient's decision to leave therapy, it reflects a breakdown in the delivery of the treatment (4)

and means that the patient did not receive the contracted treatment or the potential benefit of a worked-through termination (5). Patient dropout results in inefficient use of treatment personnel, particularly in the public sector and other managed health care settings. Furthermore, unexplained patient dropout can be demoralizing to therapists.

The economics of psychotherapy have become particularly salient in the present climate of cost containment and managed health care (6, 7). Partly in response to economic forces that affect medical care delivery in general and partly in recognition of the possible efficacy of brief psychotherapy for a variety of disorders, interest has grown in the refinement and use of brief psychotherapy (8–17). Several specific methods of brief psychotherapy have been developed (8–12, 14–17).

Mann (10), the developer of time-limited psychotherapy, has asserted that his approach not only is clinically effective but also offers advantages such as a lower dropout rate. In this paper we will report a finding consistent with Mann's claim; namely, that the dropout rate from a form of time-limited psychotherapy based on Mann's model was lower than the dropout rates from two other types of individual psychotherapy offered in the same setting.

METHOD

The present report is part of a larger study that was designed to examine the common clinical assumption that patient dropout early in psychotherapy indicates treatment failure. The results of the broader study, including a detailed description of the methodology, are available elsewhere (18). Only aspects of the study relevant to the present report are described here.

Setting and Patients

The study was done at a large, urban, university-affiliated community mental health center (CMHC) in the northeastern United States. At the time of the study, the CMHC provided several types of outpatient treatment, including group psychotherapy, family psycho-

TABLE 1. Demographic Characteristics of 149 Clinic Patients Referred for Individual Psychotherapy

Characteristic	Number	Percent
Sex		
Male	67	45
Female	82	55
Age (years)		
16–20	14	9
21–29	80	54
30–39	33	22
40–80	22	15
Race		
Black	13	9
White	131	88
Other	5	3
Education		
Less than high school	25	17
High school degree	67	45
College degree or more	57	38
Marital status		
Never married	84	56
Married	28	19
Divorced, separated, or widowed	37	25

therapy, and three forms of individual psychotherapy, to patients who could not afford private treatment.

The patients studied (N=149) were selected from all patients who 1) were 18 years old or older, 2) were new to the CMHC during two fiscal years, 3) completed the initial evaluation process or were referred directly to psychotherapy from another facility, and 4) were referred for individual psychotherapy. Three hundred seventy-six patients met these four criteria. However, due to time constraints, the cases of new patients who were referred to long-term individual psychotherapy during the first 6 months of the first fiscal year (N=73) were not reviewed for inclusion in the study. Therefore, the actual number of cases reviewed for possible inclusion was 303.

Two sets of clinical and course of treatment inclusion/exclusion criteria were applied to clinic charts to select the study group from the patients referred for individual psychotherapy. The main purpose of the clinical exclusion criteria was to identify patients whom therapists commonly regard as good candidates for psychotherapy. Such a study group was desired to enhance the clinical relevance of the study. The clinical exclusion criteria were patient characteristics that are often regarded as poor prognostic signs for psychotherapy. Patients were excluded who carried a primary DSM-III intake diagnosis of substance abuse disorder, mental retardation, or an organic mental disorder or who had histories consistent with a chronic psychotic condition. The course of treatment criteria excluded patients who 1) did not attend any therapy sessions after being referred to treatment, 2) were in an active course of individual psychotherapy at the time of the study, and/or 3) had received another form of psychotherapy (e.g., group or family) concurrently. The demographic characteristic of the final study group of clinic patients (N=149) are presented in table 1.

Referral to Psychotherapy

New clinic patients were typically assigned to an evaluating clinician who met with them for one to three sessions to arrive at an understanding with the patient of what he or she wanted from therapy and the type of treatment that seemed most appropriate. Two options for individual psychotherapy were available: long-term psychotherapy or brief psychotherapy. Those referred to brief psychotherapy could be treated either with Mann's time-limited psychotherapy or with non-specific, brief, psychodynamically oriented psychotherapy that lasted about 3–4 months but had no specific termination date.

Assignment to long-term or brief individual psychotherapy generally was a function of patient interest, therapist availability, and the evaluating clinician's judgment. However, clinic policy was that if patients who were severely depressed, suicidal, psychotic, or significantly at risk to become psychotic were referred to individual psychotherapy, they would be referred to long-term psychotherapy and not brief psychotherapy. Although it was not clinic policy to do so, staff also tended to refer patients whom they regarded as very good psychotherapy candidates to long-term psychotherapy. For patients assigned to brief therapy, the therapist could decide whether to use time-limited psychotherapy; however, therapists were encouraged to use time-limited psychotherapy with all patients referred to brief psychotherapy. Variables that may have influenced the decision to use time-limited psychotherapy were not measured or controlled in the study.

Types of Psychotherapy

Open-ended psychotherapy. Long-term, open-ended psychotherapy was the most typical type of individual psychotherapy offered at the clinic when the study was done. The defining feature of open-ended psychotherapy was the absence of a specified duration; the patient could continue until he or she decided to terminate (either independently or in conjunction with the therapist) or until the therapist left the clinic. The possible duration of open-ended psychotherapy with the same therapist ranged from about 6 months to 2 or more years, depending on how long the therapist was associated with the clinic.

The most definite termination information that might be given at the outset of open-ended psychotherapy was that the therapist would be leaving at some designated future time. However, not all open-ended psychotherapy patients were given such information. Clinic records did not reliably indicate how often termination was discussed with open-ended psychotherapy patients at the outset. Our impression is that most patients were not given this information. Open-ended psychotherapy as taught and advocated at the clinic was a psychodynamically oriented, flexible psychotherapy; the median session frequency was once a week.

Brief psychotherapy. The main difference between how brief psychotherapy and open-ended psychotherapy were conducted at the clinic was that brief psychotherapy patients were told at the beginning of therapy by the therapist or the evaluating clinician that their treatment was expected to last about 3–4 months. Like open-ended psychotherapy, a definite termination date was not set at the beginning of brief psychotherapy, and, in practice, the precise end of psychotherapy was negotiable depending on the therapist's judgment of what was indicated clinically and what the patient wanted. For the purposes of this study, if a brief psychotherapy treatment went beyond 16 sessions, it was still counted as brief psychotherapy because we were interested in the effect of how the treatment contract was set up at the beginning.

Time-limited psychotherapy. At the time of the study, Mann's time-limited psychotherapy (10–12) was being taught and developed as the clinic standard for brief psychotherapy. Some of the therapists at the clinic were taking or had recently taken a didactic seminar on the time-limited psychotherapy method. Therefore, the therapists who used time-limited psychotherapy were relative beginners with the model, although their overall clinical experience varied widely.

Time-limited psychotherapy differed from brief psychotherapy most clearly in how the ending of the psychotherapy was addressed when the treatment started. For all patients given time-limited psychotherapy, documentation in the clinic chart indicated that the therapist set a specific number of sessions and sometimes a termination date with the patient when treatment began. In most time-limited psychotherapies, the patient was offered a contract of 12 sessions, Mann's time-limited psychotherapy standard. However, therapists sometimes deviated from the 12-session model. For example, therapists who had fewer than 12 weeks remaining at the clinic offered patients fewer than 12 sessions. Cases were included in the time-limited psychotherapy group in the present study if the number of sessions offered to the patient ranged between eight and 16.

In addition to a 12-session contract, a second fundamental principle of Mann's time-limited psychotherapy is to identify a central issue in treatment and to communicate this issue explicitly to the patient when the therapy starts (10–12). A central issue or focus was identified in some cases in the study group. However, the extent to which the focus was formulated according to time-limited psychotherapy principles (10–12) and adhered to throughout the psychotherapy probably varied. On the basis of a systematic review of therapists' treatment summaries in the clinic charts, we determined that the only time-limited psychotherapy principle always implemented by therapists who used time-limited psychotherapy was the explicit setting of a specified number of sessions at the outset of psychotherapy.

TABLE 2. Dropout Rates of 149 Patients Given Time-Limited, Brief, or Open-Ended Psychotherapy

Type of Psychotherapy	Patients Who Dropped Out of Therapy		Patients Who Remained in Therapy	
	N	%	N	%
Time-limited (N=34)	11	32	23	68
Brief (N=46)	31	67	15	33
Open-ended (N=69)	42	61	27	39

Therapists and Termination Categories

Patients were treated either by trainee (74.5% of the patients, N=111) or staff (25.5%, N=38) therapists. Forty-three trainees and 20 staff therapists treated the patients in the study group. The psychotherapy experience of trainees ranged from 0 to 3 years. The experience of staff therapists doing psychotherapy ranged from less than 1 year to more than 10. Twenty-seven of the therapists were psychiatrists, 18 were nurses, nine were social workers, five were mental health workers, and four were psychologists. The number of cases per therapist ranged from one to 10, with a median of three. Nine therapists treated patients in time-limited psychotherapy only, 15 therapists had patients in both time-limited psychotherapy and at least one of the other forms of individual psychotherapy, and 39 therapists treated patients in brief psychotherapy and/or open-ended psychotherapy but not in time-limited psychotherapy. Both staff and trainee therapists were supervised. The prominent orientation among supervisory personnel at the clinic was psychoanalytic psychotherapy.

Clinic records were used to determine how a patient terminated psychotherapy. Patients were classified as having dropped out of therapy (N=84) or as remaining in therapy (N=65) according to a coding system developed for the study (18). The dropout group consisted of patients who unilaterally and abruptly stopped keeping appointments, either with or without notice to the therapist but without the therapist's concurrence. The patients who remained in therapy continued to a preset or planned termination date (mutually agreed on by patient and therapist) or until the therapist initiated termination.

RESULTS

Dropout Rate by Type of Psychotherapy

The dropout rate for time-limited psychotherapy was 32%, about one-half the rate for brief psychotherapy (67%) and the rate for open-ended psychotherapy (61%) (see table 2). The association between whether a patient dropped out of or remained in therapy and type of psychotherapy (time-limited, brief, or open-ended) was significant ($\chi^2=10.81$, df=2, p<0.005),

TABLE 3. Relationship of Dropout Rates to Severity of Impairment for 149 Patients Given Time-Limited, Brief, or Open-Ended Psychotherapy

Type of Psychotherapy	Least Severe					Moderately Severe					Most Severe				
		Dropped Out		Remained			Dropped Out		Remained			Dropped Out		Remained	
	N	N	%	N	%	N	N	%	N	%	N	N	%	N	%
Time-limited (N=34)	19	6	32	13	68	14	4	29	10	71	1	1	100	0	0
Brief (N=46)	23	16	70	7	30	22	15	68	7	32	1	0	0	1	100
Open-ended (N=69)	21	13	62	8	38	37	21	57	16	43	11	8	73	3	27
Total (N=149)	63	35	56	28	44	73	40	55	33	45	13	9	69	4	31

indicating that the proportion of patients who dropped out or remained differed by type of psychotherapy.

The results of chi-square tests done to see if there was an association between termination group and type of therapy for time-limited psychotherapy compared with brief psychotherapy (corrected χ^2=8.27, df=1, p<0.005) and for time-limited psychotherapy compared with open-ended psychotherapy (corrected χ^2=6.32, df=1, p<0.02) indicated that the dropout rate from time-limited psychotherapy was significantly lower than the dropout rate from either brief or open-ended psychotherapy.

Patient Characteristics

Demographic features of the patients were examined to determine if the differential dropout rates could be explained by demographic differences of the patients in the three forms of psychotherapy. Chi-square tests revealed no statistically significant differences in gender, age, race, marital status, or education among the patients in the three types of psychotherapy.

To explore whether the differential dropout rates could be due to differences in patients' diagnoses, we assigned patients to one of three categories of severity of impairment using their *DSM-III* axis I and axis II discharge diagnoses. A three-category system was used because there were too few patients in some diagnostic groups to statistically examine the potential contribution of diagnosis to dropping out. The *DSM-III* diagnoses that the analyses are based on are regarded only as gross indicators of functional impairment because the diagnoses were made by different therapists with varied backgrounds and experience and no systematic attempts were made to establish the reliability of the diagnoses. Discharge diagnoses were used because we believed that they were likely to be more accurate descriptions of the patients during the target episode of treatment than the intake diagnoses.

The three-category system used to indicate severity of impairment was 1) least severe (no diagnosis or adjustment disorder), 2) moderately severe (major depression without an axis II diagnosis, other affective or anxiety disorder with or without an axis II diagnosis, axis II personality disorder, adjustment disorder with an axis II diagnosis, or other miscellaneous categories such as bulimia and ego-dystonic homosexuality with and without an axis II diagnosis, and 3) most severe

(major depression with an axis II diagnosis, bipolar disorder, or psychosis with or without an axis II diagnosis). Table 3 presents the numbers of patients who dropped out of or remained in therapy in each severity category for each type of psychotherapy.

A three-by-three Kruskal-Wallis test (19) was used to examine the relationship between severity of impairment and type of psychotherapy because the expected cell frequencies were inadequate for a valid chi-square test. The Kruskal-Wallis statistic (corrected H=10.834, p<0.01) indicated that type of psychotherapy was significantly associated with severity of impairment. Inspection of the data revealed that 11 (16%) of the open-ended psychotherapy patients, one (3%) of the time-limited psychotherapy patients, and one (2%) of the brief psychotherapy patients were in the most severe category. This difference suggested that although time-limited psychotherapy and open-ended psychotherapy patients may have differed in severity of impairment, time-limited psychotherapy and brief psychotherapy patients did not. Ryan's procedure for pairwise comparisons with the Kruskal-Wallis test (20) confirmed this impression: no association was found between severity of impairment and type of psychotherapy when time-limited psychotherapy was compared with brief psychotherapy. However, when time-limited psychotherapy and open-ended psychotherapy patients were compared along the dimension of severity, Ryan's procedure revealed a significant difference (Z=2.77, p<0.05). Brief psychotherapy and open-ended psychotherapy patients also differed on the dimension of severity (Z=2.62, p<0.05).

The association between severity of impairment and type of psychotherapy for open-ended psychotherapy and time-limited psychotherapy patients suggested that the differential dropout rates from the two types of psychotherapy could be due to patient differences. However, for severity of impairment to account for the different dropout rates, severity of impairment would have to be positively associated with dropping out. No significant association between severity of impairment and type of termination was found (χ^2=0.965, df=2, p<0.65), suggesting that the differential dropout rates among the types of psychotherapy were not due to patient differences in severity of impairment. A chi-square test comparing types of psychotherapy and termination groups was performed without the 13 patients who were rated most severe in functional im-

pairment. The results (χ^2=11.95, df=2, p<0.003) revealed a statistically significant difference in dropout rates for time-limited psychotherapy (30% [N=10]), brief psychotherapy (69% [N=31]), and open-ended psychotherapy (59% [N=34]). Thus, the differential dropout rates among the three types of psychotherapy do not seem to have been due to patient differences in severity of impairment.

Therapist Characteristics

To explore the possibility that the differential findings in dropout rates were due to therapist differences, the proportions of trainee and staff therapists in each of the psychotherapy groups were compared. A statistically significant association was found (χ^2=13.91, df=2, p=0.001). Nineteen (41%) of the patients given brief psychotherapy, 11 (32%) of the patients given time-limited psychotherapy, and eight (12%) of the patients given open-ended psychotherapy had staff therapists. However, the therapist's status was not significantly associated with type of termination (corrected χ^2=2.39, df=1, p<0.13), indicating that the differential dropout rates for the psychotherapy groups were not due to differences in therapist status along the trainee versus staff dimension. The fact that 67% of the therapists (88% [N=30] of the patients in time-limited psychotherapy) who provided time-limited psychotherapy also performed one or both of the other forms of therapy is evidence against the possibility that unmeasured, nonspecific therapist characteristics were responsible for the differential dropout rates. When the patient dropout rates of the therapists who performed more than one other form of therapy (102 patients) were compared along the dimension of type of therapy, the dropout rate of time-limited psychotherapy patients (32% [N=8]) was significantly (χ^2=6.17, df=2, p<0.05) below the dropout rate of brief psychotherapy and open-ended psychotherapy patients (65% [N=22] and 51% [N=22], respectively). Additionally, when the work of the therapists who performed only one type of therapy was compared (47 patients), the dropout rate by type of therapy persisted (dropout rates of 33% [N=3], 75% [N=9], and 77% [N=20], respectively, for time-limited psychotherapy, brief psychotherapy, and open-ended psychotherapy). No valid chi-square test could be performed on data for these 47 patients because of small cell sizes. The fact that higher dropout rates were not significantly associated with therapist variables as measured in this study (trainee versus staff and type of therapy practice) is evidence that the differential dropout rates among the types of psychotherapy were not a function of qualities of the therapists.

Dropout Rate by Length of Therapy

To determine if the differential dropout rate was due to the possibility that time-limited psychotherapy had

fewer sessions and, therefore, presented less opportunity to drop out, means and standard deviations for the number of sessions by type of psychotherapy were examined. The mean±SD number of sessions for time-limited psychotherapy, brief psychotherapy, and open-ended psychotherapy, respectively, was 10±5.1, 7.8±7.5, and 15.4±12.8 sessions. The mean number of sessions for the patients who dropped out of time-limited psychotherapy, brief psychotherapy, and open-ended psychotherapy was 6.9±5.2, 5.3±4.6, and 10.9±9.9, respectively. By the 12th session, eight (73%) of the 11 patients who dropped out of time-limited psychotherapy, 27 (87%) of the 31 patients who dropped out of brief psychotherapy, and 32 (76%) of the 42 patients who dropped out of open-ended psychotherapy had left treatment. Additionally, a chi-square comparison eliminating the 49 patients whose treatment went beyond 12 sessions yielded χ^2=13.48, df=2, p<0.0015, and dropout rates of 36% [N=8], 73% [N=27], and 81% [N=33], respectively, for time-limited psychotherapy, brief psychotherapy, and open-ended psychotherapy. Thus, the differential dropout rates do not appear to be due to the possibility that patient dropout occurred in any significant proportion after most time-limited psychotherapy treatments had terminated.

To examine the possibility that unknown correlations contributed to the positive and robust findings of lower dropout rates with time-limited psychotherapy and obscured the effects of other variables, we performed a logistic regression analysis with the independent variables of length of treatment, type of psychotherapy (time-limited, open-ended, or brief), status of therapist (trainee or staff), and severity of dysfunction (least, moderately, and most severe). Whether the patient dropped out of or remained in therapy was the dependent variable. The results, presented in table 4, indicate that within the model described by these independent variables there was a significant overall effect: length and type of therapy were able successfully to predict almost 72% of the types of termination.

DISCUSSION

The main finding was that the dropout rate from psychotherapy that had a definite time limit was approximately one-half the dropout rate from two other forms of individual psychotherapy offered in an outpatient clinic. The finding could not be attributed to patient demographic or diagnostic characteristics, staff versus trainee therapist status, therapist practice patterns (as measured in this study), or differential lengths of the treatments. Because the study was archival and therapist and patient features could not be adequately controlled, it is possible that some unmeasured patient and/or therapist characteristics contributed to the differential dropout rates found. However, the findings were quite robust, withstood all tests of alternative interpretations that could be made with the available

TABLE 4. Logistic Regression Analysis of Whether Patients Remained in Therapy by Type of Therapy, Severity of Impairment, Length of Treatment, and Status of Therapist[a]

Independent Variables[b]	Beta	Standard Error	Wald[c]	df	R	p
Type of psychotherapy			13.34	2	0.21	0.001
Time-limited versus open-ended	1.08	0.31	12.34	1	0.25	0.00004
Open-ended versus brief	−0.26	0.28	0.89	1	0.00001	n.s.
Severity of impairment			0.84	2	0.00001	n.s.
Least severe versus most severe	0.28	0.33	0.73	1	0.00001	n.s.
Moderately severe versus most severe	0.14	0.30	0.20	1	0.00001	n.s.
Length of treatment	0.11	0.03	17.73	1	0.28	0.00001
Status of therapist[d]	−0.40	0.23	2.92	1	−0.07	0.09

[a]In step one, length was added (model $\chi^2=22.65$, df=1, p<0.00001); in step two, type of therapy was added (model $\chi^2=37.95$, df=3, p<0.00001) (overall model $\chi^2=42.05$, df=6, p<0.00001).
[b]Whether the patient remained in therapy was the dependent variable.
[c]The ratio of the coefficient of regression squared over the standard error; approximates the chi-square distribution (21).
[d]1=trainee; −1=staff.

data, and are consistent with Mann's assertion that time-limited psychotherapy has a lower dropout rate than is typical for outpatient individual psychotherapy (10). Furthermore, the findings have important clinical implications and merit examination in a prospective study in which patients are randomly assigned to different individual psychotherapy conditions.

One likely explanation for the differential dropout rates is the manner in which time-limited psychotherapy clearly differed from both brief psychotherapy and open-ended psychotherapy. Only in time-limited psychotherapy was a specific time limit explicitly set for the therapy at the start of the treatment. Making the ending explicit and definite may help reduce any patient tendencies to enact conflicts or fears about termination or the psychotherapy by dropping out. For example, it is possible that a clearly limited, short duration of psychotherapy reduces fears concerning relationship issues such as intimacy, dependency, and a regressive relationship with the therapist. A limited duration and definite ending prescribed at the beginning may provide a psychological structure that helps a patient remain in therapy even in the face of frustrating, stressful, frightening, or otherwise problematic feelings and experiences. Some patients simply may be more willing to "stick it out" when they know the psychotherapy will end soon. Alternatively, other aspects of time-limited psychotherapy, such as setting a focus, the rapid establishment of a positive therapeutic alliance, and greater therapist activity, could have had more impact on the dropout rate than the technique of setting a preset limit (10–12). However, no data were collected to examine the potential impact of such variables.

Other investigators (3, 4) have reported a lower dropout rate for a brief form of psychotherapy compared with a longer form of psychotherapy when both were offered in the same clinic. Straker (4) reported that the clinic dropout rate declined from 62% to 32% when the clinic moved from a long-term treatment orientation to a brief treatment orientation. However, he

did not offer an explanation for the change in dropout rate except to suggest that setting a time limit helped patients and therapists focus on addressable problems at hand and avoid issues of chronicity and disillusionment. Reder and Tyson (3) noted that 13% of brief treatment patients dropped out before the 6-month limit elapsed but that 41% of long-term psychotherapy patients dropped out by the end of 6 months. They assumed that the different dropout rates were due to patient variables because the more disturbed patients were selected for the longer-term psychotherapy.

The findings of Reder and Tyson are similar to those of the present study, but there are important differences. Our sample was selected to exclude more disturbed patients (i.e., patients with chronic psychoses), and severity of impairment based on diagnosis did not account for the differential dropout rates. Furthermore, in the present study a difference in dropout rate was found between the two forms of brief treatment, brief psychotherapy versus time-limited psychotherapy, as well as between time-limited psychotherapy and the longer-term, open-ended psychotherapy.

In summary, the findings of the present study are consistent with the conclusion that the technical devices of a preset termination date and a therapy duration that is brief can reduce the tendency of patients to drop out of individual psychotherapy. Because the study is based on archival data, many potentially important variables were not controlled, nor can we rule out selection biases in the patient population. Therefore, the results reported here should be generalized to other settings with considerable caution. Further research should be done to replicate these results and to elucidate psychological variables that may be affected by setting a preset termination date and making the therapy duration short. To the extent the findings are valid, the clinical implications are clear: the dropout rate from individual psychotherapy in a public clinic for appropriate diagnostic groups may be substantially reduced by using a treatment in which the number of sessions is specified and limited from the outset.

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Aftermath of the *Rogers* Decision: Assessing the Costs

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The Massachusetts Supreme Judicial Court's decision in Rogers v. Commissioner *is generally regarded as an important right to refuse treatment decision requiring maximum judicial involvement in the treatment of nonconsenting patients. Since courts and legislators in other jurisdictions have looked to* Rogers *for guidance on right to refuse treatment issues, and since some have adopted it as a model, it is essential for lawmakers to understand the economic realities of the Massachusetts experience and the commitment of resources required by this model. The authors review these realities, suggesting that there are distinct reasons for considering this particular model "cost ineffective" in preserving patients' rights.*
(Am J Psychiatry 1990; 147:1348–1352)

I n *Rogers v. Commissioner of Mental Health* (1), the Massachusetts Supreme Judicial Court held that all psychiatric inpatients, competent or incompetent, have a right to refuse treatment with antipsychotic medications except in limited emergency situations and that this right is based on the statutory and common (case) law of the Commonwealth of Massachusetts. *Rogers* held that decisions regarding use of antipsychotics with incompetent patients must be made by a judge using a "substituted judgment" analysis in the context of a full adversarial proceeding (1). The *Rogers* decision and its clinical and theoretical implications have been extensively reviewed elsewhere (2–11); a full review will not be repeated here.

By requiring a full adversarial procedure, the Massachusetts court created many practical and clinical difficulties. This article documents their nature in economic and human costs.

IMPACT AND RESPONSE

At present no one denies that *Rogers* has had a major impact on psychiatric care in Massachusetts (unpublished 1989 paper of S.K. Hoge et al.), but considerable disagreement remains regarding whether the net effect has been positive or negative (8–11). Some preliminary research results on clinical effects will be available soon from a multicenter study of this issue (unpublished 1989 paper of S.K. Hoge et al.). Information concerning more easily measured economic costs of implementing the decision, however, is now available in a survey reported in September 1988 by the legal office of the Massachusetts Department of Mental Health. This unpublished survey, titled "Report on the Department of Mental Health's Implementation of the Supreme Judicial Court's Decision in *Rogers v. Commissioner*," forms the basis for this paper. This unpublished report will be referred to in this article as the "DMH Report."

THE REPORT OF THE DEPARTMENT OF MENTAL HEALTH

The legal office of the Massachusetts Department of Mental Health, recognizing the changes in staffing and duties since the *Rogers* decision, undertook a study of the manpower effects of *Rogers*. It examined an 18-month period from July 1986 to December 1987, during which more than 2,000 *Rogers* petitions were filed by Department of Mental Health attorneys. Statistics were compiled regarding the total number of petitions filed, whether the patient accepted or refused treatment, the percentage of petitions granted or denied in each of these categories, the time required to obtain a court order, and resources (in terms of attorney, clinician, and paralegal hours) expended in pursuing such an order. Statistics on judicial time spent and costs for non-Department-of-Mental-Health counsel, independent experts, and guardians were not included.

CASELOAD

During the 18-month period in question, the Massachusetts Department of Mental Health filed petitions for *Rogers* orders in 2,273 cases, approximately 126 per month—an average of more than five for every

working day. This number is misleadingly low. The data in the DMH Report do not include Department of Mental Health patients for whom petitions might be appropriate but had not been filed because of the patient's treatment compliance or the reluctance of staff to engage in the adversarial process. In addition, the DMH Report emphasized that the survey did not include patients outside the Department of Mental Health at private psychiatric facilities, nursing homes, and general hospitals or under the care of other public agencies or private practitioners. The results of a strict application of *Rogers* in all of these settings are a matter of speculation.

The majority (70%) of Department of Mental Health petitions involving mentally ill patients were for patients who were presumed to be incompetent and were refusing antipsychotic medication. Patients who may have been incompetent but who accepted medications ("assenting" patients), estimated to be in the thousands, were in practical terms rarely the subjects of *Rogers* proceedings. Thus, not only was the number of *Rogers* cases from all sources greater than the 126 per month documented by the DMH Report, but the potential caseload from the Department of Mental Health alone was considerably larger than what was actually presented to the courts.

Of the 2,273 petitions filed during the period in question, 57 were withdrawn—presumably because the patient had been discharged from the petitioning facility before the competency hearing, the competency of the patient was reassessed, the treatment plan was altered to omit medications, or the patient started to take medications voluntarily. The DMH Report suggested that in some cases the response to medication then rendered the patient competent to consent, thus eliminating the need for further proceedings. It did not report how many of those patients for whom the petitions were withdrawn became the subjects of later petitions.

According to the data in the DMH Report, the courts granted 2,195 (99.1%) of the 2,216 petitions pursued to completion and denied the petition in 21 (0.9%) of the cases. Thus, in less than 1% of the cases was the patient's refusal of treatment granted judicial authority. Efforts to obtain follow-up information on these patients are underway. When examined in terms of whether the patients in question were refusing or accepting medications at the time of petition, the data reveal that, of the 1,514 petitions involving medication refusal, 1,493 (98.6%) were granted. All 702 of the petitions that did not involve medication refusals but involved incompetent patients who were accepting medications were granted. Approximately 25% of the 2,216 cases heard involved mentally retarded patients, and a majority of these patients were accepting their medications. Of the petitions involving the mentally ill, 70% involved patients refusing medication and 30% involved patients accepting medication. In no case involving mentally retarded or mentally ill patients who

accepted medications did the court order termination of treatment.

The vast majority of petitions (N=1,991) were handled by the probate court in conjunction with a guardianship proceeding. Of these, 894 were filed for review of an order previously entered by the probate court. The remaining 282 were filed in district courts in conjunction with commitment proceedings. The DMH Report suggested that several of the treatment plans for both mentally ill and mentally retarded patients underwent modification during the process before final approval, supposedly as a result of negotiation among parties.

MANPOWER ANALYSIS AND CALCULATION OF COSTS

The DMH Report estimated that the Department of Mental Health expended 10 hours of direct and indirect attorney time on each of 2,216 *Rogers* cases that were followed to completion. A more specific time analysis revealed the following:

1. When the patient was accepting treatment and already had a guardian, the petitioning (Department of Mental Health) attorney spent 1 to 2 hours in preparation and about 15 minutes in actual court time.

2. When the patient was presumed competent, had no guardian, and was actively refusing medication, attorney preparation took more than 5 hours, and the time spent at the hearing was often a day or more.

3. Pretrial memoranda as well as appearance at a pretrial hearing were required in some cases.

4. In cases where approval of a treatment plan was pursued in conjunction with a commitment hearing, the addition of the medication issue added at least an additional 30 minutes of hearing time and 1 to 2 hours of preparation time.

5. In total, a minimum of 10,500 attorney hours were spent in the preparation and trial of *Rogers* cases during the 18 months in question. The DMH Report equated this to 28 direct attorney hours for each working day.

6. Clinical staff are responsible for the preparation of a detailed affidavit that addresses each of the six patient-treatment factors required in *Rogers* for substituted judgment (1). The DMH Report suggested that preparation of these reports by the psychiatrist, psychologist, or social worker requires "at least a full hour of clinical staff time." Experience at our institution, which is extremely familiar with *Rogers* hearings, suggests that this is an excessively conservative estimate of the time required for preparation of these affidavits. More realistically, staff—most of whom are novices at writing such documents—would require 1 to 3 hours; additional time is needed for supervision.

7. Clinicians generally are not required to testify when affidavits are complete. In more difficult cases their testimony is required, involving at least half an hour of testimony; this is in addition to the prepara-

tion time with the attorneys for both the Department of Mental Health and the patient, as well as with the guardian or monitor. The Department of Mental Health survey found that 4,800 direct clinical staff hours were spent on *Rogers* petitions during the 18 months in question. This works out to 18 clinical staff hours per working day.

8. On average, 1–1½ paralegal hours are required to prepare each guardianship petition to be filed. The addition of a *Rogers* request adds approximately 15 minutes of preparation time. Paralegals are also responsible for follow-up notices to the parties after the hearing. The DMH Report estimated that more than 3,000 hours of paralegal time were expended on *Rogers* cases during the study period. This equals 11½ paralegal hours per working day in addition to the usual time spent on medical guardianship and other matters.

The DMH Report projected that when direct and indirect times are added the following additional manpower would be needed to implement the *Rogers* decision: eight to nine full-time attorneys, four full-time paralegals, six and a half clerks, and eight full-time clinicians. To meet these needs, the Massachusetts legislature appropriated an additional $364,000 in fiscal year 1985 and an additional $824,000 in fiscal year 1986 (personal communication from Richard Ames, General Counsel, Massachusetts Department of Mental Health).

Note that the manpower projections do not include time expenditures by all parties, including travel, waiting for proceedings to commence, preparing for cases that are never heard, affidavit preparation time, and supervision of trainees. Nor do they include the time devoted by judges, counsel for patients, guardians, and independent expert evaluators. We stress again that these statistics apply to petitions for Department of Mental Health patients—that is, patients in this substantial but limited part of the public sector. Similar and perhaps greater resources are expended on *Rogers* proceedings for patients in private facilities, general hospitals, nursing homes, the Department of Corrections, the Department of Public Health, and other agencies and organizations that treat the mentally ill. To our knowledge, statistics for those settings have not been gathered.

INTERPRETING THE DATA

The system mandated in the *Rogers* decision provides some scrutiny of clinical decisions and may bring about some element of negotiation and modification of treatment plans. However, the advice of the petitioning clinicians is ultimately followed in the overwhelming majority of cases. To assess fully the importance of these decisions, we still need to know how many of these petitions were contested and how many were resubmitted; these data are not available. Nevertheless, a number of hypotheses may explain the over-

whelming likelihood that a petition to override refusal will be granted rather than denied.

First, research in Massachusetts (12) has suggested that when asked to make commitment decisions, judges and physicians consider very similar factors. The decision often involves application of what amounts to a best interest test rather than strict adherence to the official dangerousness criteria for commitment. It is quite possible that judges, faced with an issue of substituted judgment in right to refuse treatment cases, may nevertheless exhibit some bias toward the more humanitarian (but less libertarian) traditional best interest analysis. That is, judges may opt for treatment rather than strictly applying the rights-driven substituted judgment model, in which the generally acknowledged best interest of the patient could theoretically be ignored in favor of "the right to rot with one's rights on" (5). As Appelbaum stated (4), and we can confirm, the focus in *Rogers* hearings is often on the appropriateness of treatment and not on competency.

Second, when representing clearly psychotic incompetent clients it is possible that some attorneys might yield to their own interpretation of fiduciary responsibility and present a pro forma or less-than-aggressive opposing argument. Indeed, it is our experience that responsible attorneys join physicians and judges in this ethical bind when they recognize a client's need for treatment (13).

Third, it is not at all clear that disposition of the issues raised in these proceedings is quite as devoid of the need for professional expertise as the Supreme Judicial Court suggested (1). Given evidence of responsible medical decision making, judges faced with difficult substituted judgment decisions may be more likely to defer to the judgment of treating physicians. Such a decision may be fostered because, as described elsewhere (14), there are some inherent paradoxes in substituted judgment decision making as it might apply to antipsychotic treatment.

Fourth, clinicians faced with the "adversarialization" of a formerly clinical process learn to perform as adversaries, framing their cases in the best possible light. The ability of physicians, aided by more experienced attorneys, to play the game effectively certainly contributes to the success of petitions.

Finally, in view of many clinicians' distaste for court proceedings and the extensive institutional, clinical, and personal costs of pursuing a *Rogers* petition, an efficiency model may predominate, as it does with commitment (12): clinicians may choose to pursue only those petitions likely to succeed in achieving treatment (15). Thus, difficult decisions may be diverted into other channels, such as discharge or allowing the patient to remain untreated.

ADDITIONAL COSTS

Although the DMH Report can provide us with an estimate of the direct economic costs of the process

and the expenditure of resources, the additional "noneconomic" costs of these cumbersome procedures are more difficult to assess. Such costs include the damage to the therapeutic relationship caused by the fundamental "adversarialization" of the treatment process as well as the effects of courtroom proceedings and the suffering of patients when treatment is delayed (sometimes to an extreme and substantial degree) as they await hearings. At our institution, the maximum delay for a *Rogers* hearing was 11 months, and delays of 8 to 10 weeks are now common. Throughout this time many patients suffer the effects of an intense, frightening, and debilitating illness. Concerned family members suffer with them while awaiting a treatment decision. In addition to the impact of the process on individual patients and their families, the time demands placed on clinicians in already understaffed facilities deny not only these but other patients needed treatment. Finally, the time spent in the paperwork and testimony for all these procedures must, of necessity, be subtracted from the most valuable resource in any public facility: direct time spent by the clinician with the patient (15).

Regrettably, clinicians faced with a potential *Rogers* hearing on a case may decide to discharge a treatment-refusing patient who meets minimal safety standards or to allow the patient to remain unmedicated until complete decompensation occurs, thus either making the argument for treatment more compelling at a later hearing or permitting treatment under emergency sanctions (1). This ethical quagmire permits no easy resolution.

ARE THERE BENEFITS TO MATCH THE COSTS?

These findings merit a close examination of the benefits against which these costs might be weighed. Does preservation of strict autonomy justify the potential harm—to the individual patient, his or her family, and society—of delaying treatment and engaging in a cumbersome ritual with minimal effect? The notion of the revolving door, whereby the untreated patient is discharged and then almost immediately needs to be rehospitalized because his or her basic need for treatment has been unmet, is yet another latent cost of this procedure.

More precisely, what benefits has the *Rogers* decision yielded? Some commentators have suggested that the decision has forced physicians to become more involved with their patients and discuss medication decisions to a much greater extent, that it has "tightened up" the decision making process. No data are available to confirm or deny this, but less adversarial systems accomplish the same goal (15, 16). Many others have suggested that the time required for filling out the substantial paperwork on this decision and making the required phone calls actually decreases the time spent with the patient. Certainly scrutiny of any type, whether it is psychotherapy supervision, utilization re-

view, clinical case conferences, or threat of judicial review, heightens our awareness of the details of our work. But is this slim benefit enough, given the overall clinical and monetary costs? The mainstay of successful supervision is a cooperative approach aimed at a common goal, not an adversarial process.

The data provided by the DMH Report and our own experiences and those of others with the impact of the *Rogers* decision (17–19) raise a serious question: Are the patients getting any benefit, either clinically or in terms of rights protection, out of this expenditure of scarce resources? The procedure now in place involves vast expenditures of time, money, and effort in a process that appears to have negligible practical effects on outcome. Approximately $1,000,000 was expended on the Department of Mental Health legal apparatus alone in this 18-month period; no portion of this amount was devoted to direct patient care. Alternative uses for these funds for housing and direct patient care quickly come to mind.

CONCLUSIONS

The right to refuse treatment and the concept of individual autonomy are principles worth protecting as central to our system of values. Their recognition by all physicians helps to ensure that patients are actively involved in treatment decisions whenever possible (20, 21). When the individual patient is unable to participate in the process by reason of incompetence, it is not unreasonable and, as we already noted, may indeed be beneficial to have some process of third-party scrutiny of clinical decisions. As Appelbaum (4) has noted, such scrutiny perhaps should not be reserved only for these cases but should be a part of every institutional decision making process. The patients' rights, which the *Rogers* court hoped to protect, do not appear to be particularly well served by this process, given the results revealed in the DMH Report.

It is worth noting once again that several other plans for making treatment decisions for incompetent patients have been proposed and adopted in different states (16, 21–23) in which the legislatures and courts are presumably no less reasonable or sensitive to rights than those in Massachusetts. It is perhaps the most poignant reflection of the futility of protecting patients through "adversarialization" of treatment that the more informal models actually honor more patient refusals and review more total cases than occurs under the *Rogers* decision, which is ostensibly designed to maximize protection (15). Indeed, over time, it appears that the number of refusals honored by the courts has dropped in Massachusetts. This may be the result of the inherent sensibilities of the bench and bar and the increasing skill of clinicians. The time may be right for Massachusetts and other jurisdictions to consider application of alternative models (16, 21–23). Such models would reduce all of the costs discussed here and promote prompt treatment and discharge from the

hospital of the mentally ill. In addition, this goal could be accomplished in a framework that both improves the quality of care and provides greater protection of the rights of patients to make treatment decisions.

The right to refuse treatment deserves protection; as always, at issue is the form that such protection should take. Although few of us would suggest that an absolute monetary value can be set on individual freedoms, a rational society establishes systems whereby maximum protection of rights is balanced against social and financial costs. Such is the essential economic tension in any society. The economic and clinical experience of Massachusetts in the post-*Rogers* era should be assessed by other jurisdictions as they consider the adoption of similar procedures in the name of rights protection.

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Effects of Doxepin on Withdrawal Symptoms in Smoking Cessation

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In a double-blind study, 15 cigarette smokers self-monitored 10 withdrawal symptoms. For the first 21 days (baseline), subjects received doxepin hydrochloride, up to 150 mg/day, or inert medication while continuing to smoke. On day 22, they were instructed to stop smoking; medication was continued. Withdrawal symptoms on the first 28 days of treatment (baseline and 7 days of attempted cessation) were analyzed. During cessation, subjects taking doxepin reported significantly less craving for cigarettes. Results from this study and others suggest that antidepressants may attenuate the severity of symptoms during withdrawal from addictive substances.
(Am J Psychiatry 1990; 147:1353–1357)

D uring the course of smoking cessation, cigarette smokers experience nicotine withdrawal symptoms (1–3). The expectation of having these symptoms may prevent attempts to stop smoking; the occurrence of symptoms has been associated with relapse (4, 5). Attempts to reduce withdrawal symptoms have focused largely on the use of nicotine gum. The evidence that gum, relative to placebo, reduces the intensity of withdrawal symptoms has been mixed (6–8). Our studies have examined the use of doxepin, a tricyclic antidepressant. In the first study (9), a case series comparing patients receiving doxepin to patients receiving no pharmacotherapy, the subjects who received doxepin reported less frequent and less intense symptoms when they stopped smoking cigarettes; differences in actual cessation did not occur. In a subsequent double-blind study of doxepin and inert medication (10), the subjects taking doxepin were significantly more likely

to still be abstinent 2 months after beginning cessation. The present report provides an analysis of the subjects' withdrawal symptoms during the first 4 weeks of the aforementioned double-blind study, i.e., during 3 baseline weeks in which they continued smoking and during the first week in which they attempted to stop smoking.

METHOD

The procedures for subject recruitment, enrollment, and treatment have been described previously (10). Briefly, 23 healthy adults met the following eligibility criteria: 1) they were at least 18 years of age, 2) each had made a previous unsuccessful attempt to stop smoking that was accompanied by withdrawal symptoms, 3) there was an absence of psychiatric complaints and contraindications for doxepin use, and 4) they each made a $135 deposit that was fully refundable if they stopped smoking for 7 days and kept all appointments. The protocol was approved by the institutional review board for human subjects research. Subjects were randomly assigned to receive doxepin hydrochloride (N=11) or inert medication (placebo) (N=12) after providing informed consent. Smoking cessation results have been reported for the subjects who were recruited during the initial announcement (campus notices, local newspaper and television) of the study (10). Subsequent "word-of-mouth" advertising resulted in additional subjects being placed on a waiting list; random assignment and treatment occurred several months later. Random assignment was done by an investigator who had no contact with the subjects; the randomization code was not available to the investigators who treated the subjects.

Medication began on the evening of the first appointment (day 1) and continued according to the following schedule: days 1–3, one capsule; days 4–6, two capsules; days 7–28, three capsules. Doxepin capsules contained 50 mg of active drug and were visually identical to the placebo capsules. All medication was to be taken shortly before bedtime. After the first appointment, the subjects met with one of the investigators for brief (15–30 minutes) weekly appointments. Smoking cessation was to start on the morning after the fourth

appointment, i.e., day 22, and continue to at least the fifth appointment on day 28.

Subjects self-reported on 10 withdrawal symptoms: 1) wanting or craving a cigarette, 2) irritability, 3) anxiety or nervousness, 4) difficulty concentrating, 5) restlessness, 6) headaches, 7) drowsiness, 8) gastrointestinal upset, 9) increase in appetite or weight, and 10) sleep changes. The first eight symptoms were diagnostic criteria for tobacco withdrawal in *DSM-III*. The ninth symptom, increase in appetite or weight, had been reported as a concomitant of both smoking cessation (11) and treatment with antidepressants (12). Since the design of this study, appetite increase or weight gain has become a diagnostic criterion for nicotine withdrawal in *DSM-III-R*. The tenth symptom, sleep changes, was monitored to detect changes attributable to the doxepin and because we had previously noted sleep changes in subjects after they stopped smoking. All symptoms were to be monitored at 9:00 a.m., 3:00 p.m., and 9:00 p.m. on 6-point rating scales, with a rating of 1 representing very definite absence and a rating of 6 representing very definite presence of a symptom. Only ratings of 1 and 6 were defined in words. A separate symptom report, containing the 10 symptoms, was provided for each rating; i.e., each subject completed three rating forms per day. Thus, 21 symptom reports were to be collected at each appointment. Symptoms reports from day 1 to day 21 reflected use of medication with continued smoking. During days 22–28, subjects continued their medication and attempted to stop smoking.

In order to be included in the analysis, subjects had to provide symptom reports for each of the first 7 days of attempted cessation; actual cessation was not necessary. This restriction permitted a day-to-day assessment of the time course of symptom intensity but also resulted in the loss of data from several subjects. Specifically, nine of the 11 doxepin subjects and six of the 12 placebo subjects provided complete data. Loss of subjects, particularly in the placebo condition, was probably influenced by the subjects' disappointment with their failure to stop smoking (10); i.e., they missed appointments and did not return their symptom reports.

Data obtained during the first 3 weeks of monitoring were averaged for each of the 10 symptoms to provide a mean baseline value. Data from each cessation day (days 22–28) were averaged to provide mean daily values for each withdrawal symptom. The symptom intensity reports of the doxepin and placebo groups were compared by repeated measures analysis of variance (ANOVA). Treatment condition was a between-subjects effect; time and the interaction of time with treatment condition were within-subjects effects. Significant treatment condition effects were evaluated further with simple ANOVAs for baseline and each cessation day. The significance level of within-subjects effects was adjusted by the Greenhouse-Geiser method. All tests were two-tailed, and p values less than 0.02 were considered significant. The confidence level of 0.02 repre-

sented a modified Bonferroni test for the number of planned comparisons (13). All analyses were performed with SAS programming (14).

RESULTS

The mean daily intensity of each withdrawal symptom is shown in figure 1. There was a significant treatment effect for craving (F=10.47, df=1, 13, p<0.01). Specifically, doxepin subjects reported less intense craving on days 23, 24, and 26–28 (each F>6.68, df=1, 13, each p<0.02). A significant interaction between treatment condition and time occurred with appetite (F=3.62, df=7, 91, p<0.02) (figure 1). Doxepin subjects experienced greater appetite symptoms before cessation; intensity was not increased substantially by cessation. In contrast, placebo subjects reported few changes in appetite during baseline but considerable increases during cessation. During the entire 4 weeks of the study, significant increases were reported for anxiety and appetite (each F>4.92, df=7, 91, each p<0.01) (see figure 1). As we have noted, the increase in appetite was affected by the interaction with treatment condition. Anxiety increased irrespective of treatment condition.

DISCUSSION

These results, in conjunction with our earlier report (10), provide the first evidence from a controlled study that doxepin aids smoking cessation and may do so through a reduction in the intensity of cigarette craving. Our first study (9) used an aggregate index of withdrawal and did not identify specific symptoms that were reduced by doxepin. Despite some similarities between nicotine withdrawal and dysthymia and evidence that nicotine can serve as a mood regulator (12, 15), smoking cessation studies examining the effects of antidepressants are rare. To our knowledge, only two such studies have been performed by other investigative groups. The first (16) compared use of imipramine, *d*-amphetamine, lobeline, placebo, and no medication. In that study, use of medication was not significantly associated with outcome. Furthermore, withdrawal symptoms were not monitored. More recently, Glassman et al. (17) examined the use of nortriptyline or fluoxetine in seven smokers. Both drugs were associated with successful cessation, but withdrawal symptom data were not provided. In contrast, cocaine studies have examined withdrawal and suggest that the adjunctive use of antidepressants may reduce craving (18). Thus, limited evidence supports the conclusion that doxepin (or other antidepressants) may reduce craving for cigarettes or other addictive substances. However, three considerations may limit the generalizability of our data.

The first is that all subjects who provided withdrawal data had not stopped smoking; i.e., two pla-

FIGURE 1. Mean Intensity of 10 Nicotine Withdrawal Symptoms in Nine Doxepin-Treated and Six Placebo-Treated Cigarette Smokers During Baseline (days 1–21) and Attempted Cessation (days 22–28)
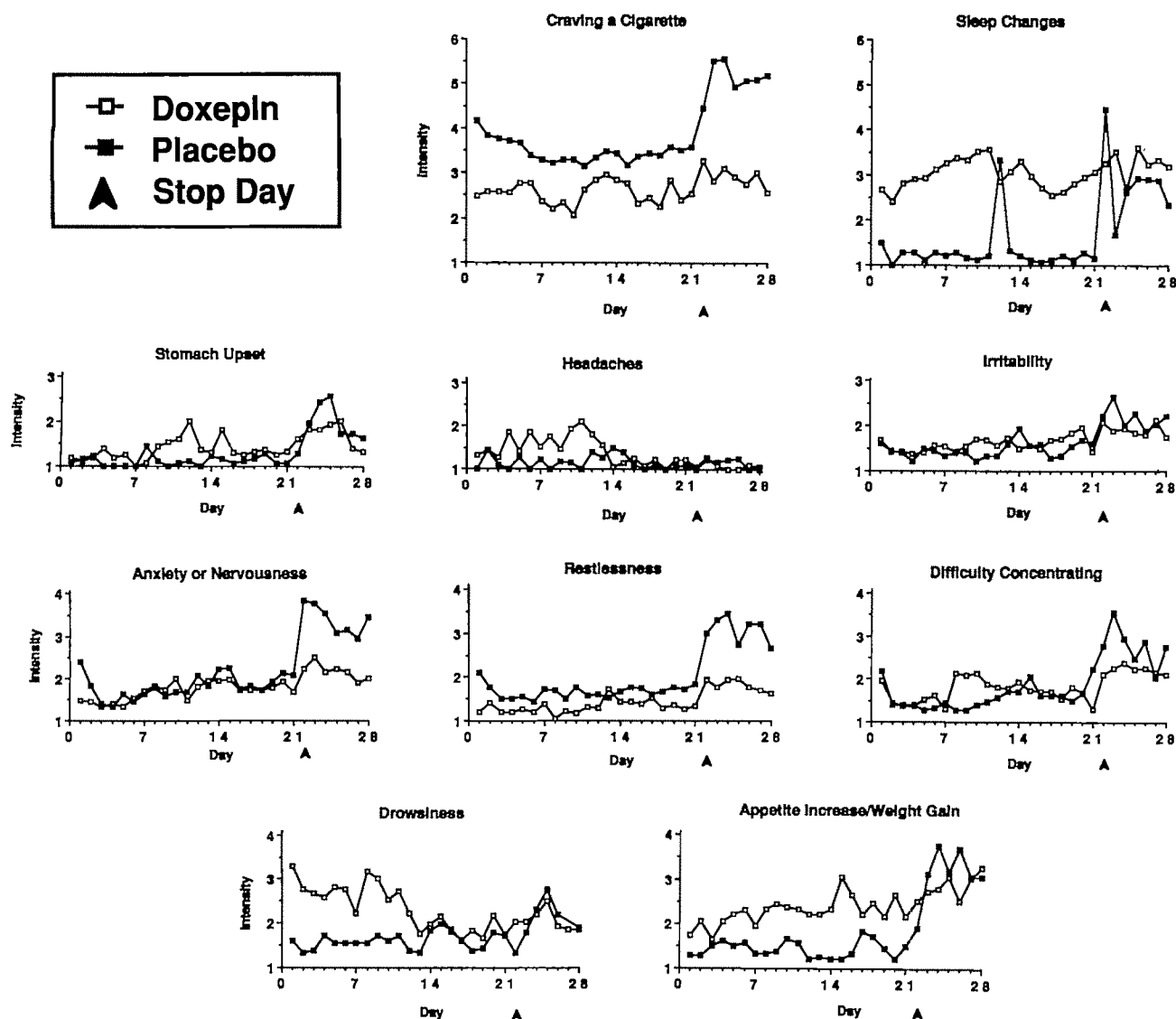
cebo subjects acknowledged that they continued smoking. Thus, differences in craving and other symptoms may have been affected by continued smoking rather than medication. However, subjects who did not achieve abstinence did achieve substantial reductions in cigarette use: by self-report, fewer than five cigarettes per day. Previous research by Hughes and colleagues (3, 7, 19) has shown that incomplete cessation of smoking did not result in significant differences in craving when compared to complete cessation. In addition, group differences in craving were significant on 5 of the 7 days after the date set for quitting.

Typically, mean differences in craving during baseline were of a 1-point magnitude on the 6-point scale; e.g., mean±SD ratings on day 17 were 2.5±1.3 and 3.4±1.7 for the doxepin and placebo conditions, respectively. During cessation, the increase for doxepin subjects was minor compared to the increase for pla-

cebo subjects. For example, the mean rating on day 28 for doxepin subjects was 2.8±1.7 (an increase of 0.3 points, or 12%, over baseline day 17), and for placebo subjects the rating was 5.1±0.8 (an increase of 1.7 points, or 50%, over baseline day 17). The larger change in the placebo group occurred despite more intense craving during baseline, which conceivably could have resulted in a ceiling effect. Considering our small sample, we are reluctant to speculate on the clinical importance of baseline differences, point changes, or percent changes in withdrawal symptoms. However, we believe the data indicate that doxepin, relative to inert medication, reduced craving during cessation. Furthermore, in light of our earlier report that use of doxepin was significantly associated with successful cessation (10), these data, if supported by future research, may have clinical relevance.

A second consideration is attrition and our small

sample size. As noted earlier, complete withdrawal data during attempted cessation was provided by only six of the 12 placebo subjects and nine of the 11 doxepin subjects. We hypothesize that the greater attrition in the placebo condition may have masked some of the benefits of doxepin. Specifically, subjects receiving inert medication may have failed to keep appointments because of their continued smoking, which may have been due to withdrawal symptoms. Although this is a speculative hypothesis, other investigators have documented the importance of withdrawal symptoms during cessation attempts (4, 5).

Our sample size also raises statistical considerations. While the small sample does not detract from the robustness of our significant results, the power to detect differences between the doxepin and placebo conditions was limited; i.e., the power was approximately 0.25 for detecting differences at a significance level of less than 0.05 (20). As shown in figure 1, several differences between conditions were suggested (e.g., drowsiness and sleep changes during baseline and restlessness during cessation), and these might have affected the impact or acceptability of doxepin. In addition, the rapid onset of appetite increases during baseline might have lessened the suitability of doxepin for some subjects. The increase in appetite may be particularly problematic in light of research indicating that weight concerns can affect smoking initiation and maintenance, as well as relapse (21–23). As noted in our earlier report (10), the maximal doxepin dose of 150 mg/day was sometimes difficult to maintain because subjects complained of side effects. Side effects, such as an increase in sleep, can negatively affect both adherence to and maintenance of the medication blind required by a study. Larger studies with more than a single active medication are needed to determine whether these effects are, in fact, important or modifiable by altered dosage regimens.

A final consideration in the evaluation of doxepin for smoking cessation is the contribution of negative affect to successful or unsuccessful cessation. Glassman et al. (24) reported that 61% of their subjects had histories of major depression and that clonidine was significantly less effective among these subjects. Other investigators have reported that depressive symptoms hamper successful cessation and are associated with relapse after cessation has occurred (16, 25, 26). In addition, anxiety has been shown to be an important correlate of smoking (27, 28). Therefore, doxepin, with both anxiolytic and antidepressant properties (29), may prove to be a suitable pharmacologic aid for many smokers.

In conclusion, the present results suggest that doxepin reduces cigarette craving among newly abstinent smokers. Replication with larger samples is needed. In addition, future pharmacologic research must examine competing biochemical hypotheses, elucidate dose-response relationships, evaluate medication effects on long-term cessation, and determine the role of mood and mood disorders in successful, sustained cessation.

Such research may provide smokers who wish to quit with more effective methods to achieve this goal.

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Brain Neurotransmitter Changes in Three Patients Who Had a Fatal Hyperthermia Syndrome

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The authors examined the autopsied brains from three patients who had a fatal hyperthermia syndrome. There was marked hypothalamic noradrenaline depletion in all three patients, severe brain choline acetyltransferase deficiency with nucleus basalis cell loss in two patients, and mild to moderate brain choline acetyltransferase loss in one patient. Striatal dopamine metabolite/dopamine ratio was below normal in two patients and not elevated, as would be expected after short-term neuroleptic administration, in the third. This suggests that reduced capability (aggravated by the cholinergic deficit) of the nigrostriatal dopamine system to respond adequately to stress and/or neuroleptic-induced receptor blockade may be important in the development and course of fatal hyperthermia syndrome.

(Am J Psychiatry 1990; 147:1358–1363)

Since 1874 (1) there have appeared in the medical literature reports of patients afflicted with a syndrome consisting of psychiatric changes and a severe disturbance of motor functions in the form of either agitation or inhibition, the latter sometimes resulting in a state of catatonic stupor. In addition to the catatonic symptoms, in a small group of such patients, there were organic symptoms consisting of severe circulatory disturbance and exsiccosis followed by a complete breakdown of functions of the autonomic nervous system, with sweating, tachycardia, and fatal hyperpyrexia (temperature up to 42 °C). This syndrome, often described in young, acutely psychotic in-dividuals, has been most frequently called lethal or fatal catatonia (2, 3) or, more recently, acute life-threatening catatonia (4, 5).

Since the era of neuroleptic drug administration began, it has been assumed that this condition can also be caused by neuroleptic drugs; hence, it has been called neuroleptic malignant syndrome (6). Neuroleptic malignant syndrome may, in fact, represent an iatrogenic form of fatal catatonia. Because it is practically impossible to make a differential diagnosis between the two conditions with absolute certainty, for the purpose of our study we refer to this syndrome of uncertain etiology as the fatal hyperthermia syndrome.

Although the pathophysiology of fatal hyperthermia syndrome is unknown, much circumstantial evidence suggests the possible involvement of the brain dopamine system. Thus, the syndrome has been associated with administration of drugs causing dopamine blockade (neuroleptics [7]) or dopaminergic depletion (α-methyltyrosine and tetrabenazine [8]) or with abrupt withdrawal of dopaminergic drugs (L-dopa, bromocriptine, and amantadine [9–11]). Moreover, the clinical features of fatal hyperthermia syndrome have been reversed in some patients by the use of dopaminergic agonists (L-dopa, bromocriptine, and amantadine [12, but see also 13]).

To our knowledge there has been no information on the status of the major neurotransmitter systems in the brains of patients with fatal hyperthermia syndrome. We describe the results of our study of the behavior of the brain dopamine, noradrenaline, and acetylcholine systems in the autopsied brains of three patients who had fatal hyperthermia syndrome, clinically diagnosed as fatal catatonia (cases 1 and 2) and neuroleptic malignant syndrome (case 3). The clinical and neuropathological findings, especially with regard to skeletal muscle involvement in two of the patients (cases 1 and 2, from the University of Graz), have been described previously (5, 14).

CASE REPORTS

Case 1. Approximately 2 weeks before admission to the hospital, Ms. A, an apparently normal 16-year-old female

high school student, suddenly developed restlessness, an unusual manner of talking, thought disturbance, abnormal behavior, and depression and was diagnosed independently by two psychiatrists as suffering from acute psychosis. Several days before admission she received one injection of fluphenazine decanoate, 25 mg i.m. A few days later she developed a temperature that reached 39.5 °C, ceased talking, remained in bed, and had no further contact with her surroundings.

On the day of admission, Ms. A showed some psychomotor restlessness, but thereafter she became unresponsive to verbal or other stimuli. She remained in a state of catatonic stupor until she died 35 days later. Her neurological status was normal with the exception of mild muscular rigidity. Her serum creatine phosphokinase level was 3,807 U/ml (normal range is up to 80 U/ml). During the first 2 weeks of treatment she received chlorpromazine and promethazine. From day 14 to day 25 she received 30 mg/day of fluphenazine dihydrochloride. ECT (eight treatments) and antibiotics were also given. She was fed by gastric tube and intravenous infusions. During the first 30 days, her temperature fluctuated between 38 and 40 °C, from day 31 to day 33 it was between 39.5 and 41 °C, and on day 34 and day 35, when death occurred, it rose to 42 °C. She sweated heavily and her heart rate ranged from 110 to 170 bpm. She died of cardiac failure.

Case 2. Mr. B, a 24-year-old man, was apparently normal until some weeks before hospital admission, when he suddenly developed restlessness, personality changes, and anxiety and lost contact with his surroundings. On admission to the hospital he was in a state of acute psychosis, with psychomotor unrest, disturbance of thought, delusions, and anxiety. He had little contact with his surroundings and no insight into his illness. His temperature was 36.7 °C.

On the first, second, and fifth day of his hospital stay, clopenthixol, 75 mg i.m., was administered. From day 6 to day 39, fluphenazine dihydrochloride, 30 mg/day, was given. Three days after admission Mr. B developed catatonic stupor with waxy flexibility and an increase of his temperature to 38 °C. Additional treatment consisted of intravenous feeding by gastric tube, ECT (15 treatments), and hemodialysis for kidney failure. On days 2–17 his temperature ranged from normal to 38 °C. During this time the patient's condition improved for several days. He was responding to treatment and also took food by mouth. Then he went into a stupor again. On days 18–38 his temperature fluctuated and went as high as 40 °C; on days 39–46 it was about 38 °C, and on days 47 and 48 it was over 40 °C. Shortly before Mr. B died, his temperature reached 42 °C, his heart rate ranged from 100 to 170 bpm, and his serum creatine phosphokinase level was up to 5,000 U/ml. The patient died of pulmonary edema and cardiovascular failure on day 48.

Case 3. Ms. C, a 54-year-old woman with a history of chronic undifferentiated schizophrenia, was admitted to the hospital in a comatose state, with fever (maximum temperature of 41.5 °C), tremor, and generalized "lead-pipe" rigidity. Five months before admission she had received treatment with 150 mg of pipotiazine palmitate (a long-acting depot phenothiazine) every 2 weeks, phenelzine sulfate (a monoamine oxidase inhibitor [MAOI]), 15 mg twice a day, and benztropine mesylate, 0.5 mg four times a day. Two days before admission she had received 100 mg of pipotiazine palmitate, 75 mg of chlorpromazine, and phenelzine. On the day of admission, Ms. C was given a cooling blanket and benztropine, 2 mg i.v. The following day she was given

two 500-mg doses of oral carbidopa/L-dopa. Two days later she became afebrile and the rigidity had improved. However, she died 3 days after admission as a result of ventricular fibrillation.

No evidence was obtained, either by direct immunofluorescence or cell culture methods, for the presence of herpes simplex virus types I and II in samples of the brains (temporal cortex and hippocampus) of these three patients.

METHOD

At autopsy one-half of each patient's brain was frozen (at −80 °C) for biochemical study, and the remaining half was placed in formalin fixative for neuropathological analyses. Specimens from selected areas were embedded in paraffin and stained with hematoxylin and eosin, Masson's trichrome, cresyl violet, Luxol fast blue, and Holzer's stain for glial fibrils. Autopsied brains of two groups of nonneurological control patients with mean±SD ages of 22±4 years (N=5) and 52±3 years (N=9) were also obtained. The intervals from death to freezing were less than 24 hours for the control patients and the fatal hyperthermia syndrome patients. Amine neurotransmitters and metabolites were measured by using minor modifications of the high-pressure liquid chromatography electrochemical detection procedure of Felice et al. (15). The cholinergic marker enzyme choline acetyltransferase was measured by the procedure of Fonnum (16). Dopamine D_2 receptor binding was measured in a filtration binding assay with minor modifications of the procedure of Seeman et al. (17), using 10 concentrations of [^{3}H] spiperone (20–1000 pM). Nonspecific binding was determined using 10-μM sulpiride. Neuroleptic (fluphenazine-like) immunoreactivity was determined in specimens of caudate from our fatal hyperthermia syndrome patients and two control subjects by the Squibb iodine-125 radioimmunoassay procedure (samples analyzed by J-F. Tu, Squibb and Sons, New Brunswick, N.J.).

RESULTS

The brains of all three fatal hyperthermia syndrome patients were grossly normal without any signs of encephalitis. Microscopic analyses revealed no abnormalities in any of these three brains in the hypothalamus, cerebral cortex, basal ganglia, thalamus, substantia nigra, pons, and medulla. The patients in cases 1 and 2 showed a marked loss of large neuronal cell bodies in the nucleus basalis of Meynert, karyopyknosis of a few neuronal cells, and spongiform changes in the neuropil. However, no senile plaques or neurofibrillary tangles in the cerebral cortex or hippocampus were noted. The nucleus basalis was within normal limits in patient 3. Sections of the cerebellum

TABLE 1. Neurochemical Indices in the Autopsied Brains of Three Patients Who Had a Fatal Hyperthermia Syndrome and of Control Subjects of Similar Age

Neurochemical Index and Brain Region	Young Control Subjects (N=5)		Young Patients With a Fatal Hyperthermia Syndrome		Older Control Subjects (N=9)		Older Patient With a Fatal Hyperthermia Syndrome (Case 3)[a]
	Mean	SD	Case 1	Case 2	Mean	SD	
Dopamine (ng/mg of tissue)							
Caudate	7.32	3.19	6.84	6.41	4.20	1.41	4.25
Putamen	9.23	3.06	8.47	7.36	5.64	1.87	8.65
HVA (ng/mg of tissue)							
Caudate	4.60	1.70	5.36	2.13^b	4.61	0.56	2.20
Putamen	8.05	2.38	7.50	3.65^b	8.04	2.94	2.15^b
HVA-dopamine (molar) ratio							
Caudate	0.67	0.46	0.66	0.28	0.97	0.11	0.44^b
Putamen	0.87	0.54	0.75	0.42^b	1.29	0.56	0.21^b
[^{3}H]Spiperone binding							
Caudate							
B_{max} (fmol/mg of protein)	135	16	90^b	102^b	95	18	88
K_d (pM)	54	33	479^b	418^b	106	50	239^b
Putamen							
B_{max} (fmol/mg of protein)	131	23	87^b	102	101	9	117^b
K_d (pM)	122	152	518^b	313	45	39	310^b
Noradrenaline (ng/mg of tissue)							
Hypothalamus	1.45	0.72	0.33^b	0.28^b	1.31	0.50	0.63^b
Fluphenazine-like immunoreactivity (ng/mg of tissue)							
Caudate	—	—	13.2^b	1.9^b	—	—	5.1^b
Choline acetyltransferase (nmol/mg of protein/10 min)							
Caudate	39.1	9.2	0.5^b	0.6^b	36.7	13.2	10.0^b
Putamen	50.0	10.8	$<0.1^b$	0.3^b	56.5	14.3	36.8^b
Cerebral cortex							
Area 10	1.30	0.19	$<0.01^b$	0.75	1.07	0.26	0.91
Area 21	1.20	0.30	$<0.01^b$	0.55^b	1.20	0.26	0.91
Area 7b	1.26	0.29	$<0.01^b$	0.16^b	1.22	0.28	1.06
Area 17	0.73	0.32	$<0.01^b$	0.13^b	0.73	0.18	0.56

[a]Received a monoamine oxidase inhibitor in addition to other treatments.
[b]Outside the range of the control group.

of this patient showed some sclerotic Purkinje cells, whereas others, in a patchy manner, showed deep eosinophilia with pyknotic nuclei. Histological analysis of the cerebellum of patients 1 and 2, however, failed to disclose any abnormal changes.

To remove any influence of age on neurotransmitter levels, the neurochemical data on the control subjects were divided into two sets: one set for the young group (22±4 years) for comparison with patient 1 (age 16) and patient 2 (age 24) and one set for the older control group (52±3 years) for comparison with the older fatal hyperthermia syndrome patient (age 54).

As shown in table 1, dopamine values in the three patients with fatal hyperthermia syndrome were within the normal range in the striatum (caudate and putamen). Levels of homovanillic acid (HVA) were markedly reduced—by 50%-70%—in both the caudate and putamen of patients 2 and 3 but were normal in the striatum of patient 1. [^{3}H]spiperone binding density (B_{max}) in the caudate nucleus was slightly below the lower limit of that of the control subjects in the two young fatal hyperthermia syndrome patients but was normal in the older patient. In the putamen, [^{3}H]-

spiperone binding density in patient 1 was below control levels (−33%), but it was normal in patient 2 and slightly elevated in the older patient (+16%). The affinity constants (K_d) were markedly higher than the control values in all three fatal hyperthermia syndrome patients in both striatal subdivisions, most likely because of the presence of residual neuroleptic drugs, as indicated by the high levels of neuroleptic (fluphenazine-like) immunoreactivity in the caudate. Levels of noradrenaline were markedly reduced in the hypothalamus of all three fatal hyperthermia syndrome patients (patient 1, −77%; patient 2, −81%; patient 3, −52%).

Choline acetyltransferase activity was profoundly reduced—by 90% or more—in the striatum and cerebral cortex (table 1) as well as in the limbic brain regions, cerebellum, and diencephalon (data not shown) in patient 1. Choline acetyltransferase values were also profoundly reduced in patient 2 throughout the brain, with the exception of the frontal (area 10) and temporal (area 21) cortex, in which moderate reduction of enzyme activity was present. Brain choline acetyltransferase values in the older fatal hyperthermia syndrome patient were within normal limits in the cerebral cortex but were be-

low the lower limit of the control values in the striatum (table 1) and also in the hippocampus and globus pallidus (data not shown).

DISCUSSION

The most striking neurochemical changes observed in our study included an apparent lack of up-regulation of striatal dopamine activity in the two young fatal hyperthermia syndrome patients and possibly in the older patient, marked reduction in hypothalamic noradrenaline in all three patients, and severely reduced brain choline acetyltransferase activity in the two young patients and a moderate reduction in the older patient.

The cerebellar neuronal degeneration observed in one of our three fatal hyperthermia syndrome patients was most likely a consequence of the hyperthermia (18). In contrast to the report of Horn et al. (19), the hypothalamus in our three patients showed no histological abnormalities, as also reported by others (18, 20). The absence of any significant pathological changes in other brain areas, with the exception of the nucleus basalis, is in agreement with similar negative findings reported in the literature (21).

Concentrations of noradrenaline were markedly reduced in the hypothalamus of all three patients. Since noradrenaline in the mammalian anterior hypothalamus is involved in the regulation of body temperature (22), it is likely that the noradrenaline depletion was a consequence of the hyperthermia and/or attendant stress in these patients. In this regard, in experimental animal studies noradrenaline turnover and release in the hypothalamus are increased and the level decreased following acute exposure to heat (22 and unpublished observations of Meyers et al.) and other acute stressors (23).

The normal or nearly normal levels of striatal and hypothalamic dopamine, striatal D_2 dopaminergic receptor binding, and substantia nigra cellularity (and dopamine concentration, data not shown) provide no evidence that a brain dopamine or dopamine receptor deficiency is responsible for fatal hyperthermia syndrome. However, the data obtained from patients 1 and 2 provide evidence, as previously suggested by clinical considerations (7, 24, 25), for abnormally low functional activity of the brain dopamine system. This is indicated by the reduced level of the dopamine metabolite HVA and, therefore, the subnormal HVA-dopamine ratio (an index of dopaminergic activity) in the striatum of patient 2 and the lack of an elevated HVA-dopamine ratio in patient 1; this would normally be expected during the first weeks of neuroleptic-induced dopamine receptor blockade and the consequent activation of presynaptic dopamine neuron activity (26–30). (Although patient 3 also had markedly reduced levels of striatal HVA, this may have been due in part or in toto to treatment with the MAOI.) It can thus be suggested that reduced capability of the brain

dopamine system to respond adequately to stress (fatal catatonia, cases 1 and 2) and/or neuroleptic-induced postsynaptic receptor blockade (neuroleptic malignant syndrome, case 3) may have been a characteristic feature of our fatal hyperthermia syndrome patients. This possibility is also supported by the recent observation of markedly reduced (−60%) HVA levels in the CSF of eight patients having the clinical features of neuroleptic malignant syndrome (25). Significantly, the HVA levels in the CSF of these patients were decreased both during the active phase of the syndrome and after the recovery phase (up to 129 days), suggesting that reduced dopaminergic function may have preceded the episodes of neuroleptic malignant syndrome.

As shown in table 1 for the striatum and cerebral cortex, activity of the specific cholinergic marker enzyme choline acetyltransferase was profoundly reduced, from −80% to −99%, in many brain areas of patients 1 and 2 and, to a lesser degree, in several analyzed brain regions of patient 3. However, no changes in other enzymes unrelated to cholinergic neurons (glutathione peroxidase, GABA aminotransferase, glutamate dehydrogenase) were observed (data not shown). The reduction in choline acetyltransferase in the cerebral cortex and limbic brain areas in patients 1 and 2 was most likely due to the marked loss of large cell bodies in the nucleus basalis, which provides much of the cholinergic innervation to the cerebral cortex and limbic brain areas (31).

Loss of the large, presumably cholinergic, cell bodies of the nucleus basalis has been previously described in a larger sample of patients with schizophrenia (32). Several of these neuroleptic-free patients died of the cardinal symptoms of hyperthermia and catatonia, whereas others did not develop hyperthermia (33, 34). Conceivably, then, the brain cholinergic abnormality in our fatal hyperthermia syndrome patients could have been due to a preexisting (developmental?) dysfunction or a combination of factors, including hyperthermia and/or neuroleptics. On the basis of evidence suggesting the involvement of the brain cholinergic system in cognition (35), some behavioral abnormalities would have been expected in our patients 1 and 2 if the severe cholinergic deficiency actually preceded the fatal hyperthermia syndrome. However, apart from the fact that the general validity of the cholinergic hypothesis is still debated (36), the functional effects on cognition of cholinergic deficits in the brains of young individuals (in our cases, 16 and 24 years old) versus deficits developing later in life in the senescent brain (as in patients with senile dementia and Alzheimer's disease) are unknown.

CONCLUSIONS

From our data we propose that striatal dopamine dysfunction accompanied by brain cholinergic hypoactivity may represent one of the factors predisposing some individuals to fatal hyperthermia syndrome.

Much pharmacological and neurochemical evidence indicates that an intrinsic cholinergic neuronal system has control over striatal dopamine release, with muscarinic cholinergic activation producing increased release of dopamine (37). This cholinergic influence is likely to play a crucial role in the neuroleptic activation of striatal dopamine turnover, as evidenced by the reversal of the effects of neuroleptics (including catalepsy) by anticholinergic drugs (38). The observed lack of the expected increase in striatal dopamine metabolism (e.g., increased HVA-dopamine ratio) in our patients who received neuroleptic drugs (cases 1 and 2) may therefore have been caused by a preexisting dopaminergic abnormality exacerbated by a profound striatal cholinergic (choline acetyltransferase) deficit, resulting in a lack of cholinergic activation of the dopamine neurons as a normal response to the neuroleptic blockade of dopamine receptors. By analogy, the reduction in choline acetyltransferase in the hypothalamus may also have been involved in the disturbed dopaminergic temperature control that has been postulated as a factor in fatal hyperthermia syndrome (39).

We suggest that future studies should devote special attention to possible dopamine and acetylcholine abnormalities in fatal hyperthermia syndrome and also to clarification of the relative risk of fatal hyperthermia syndrome in brain cholinergic deficiency syndromes such as Alzheimer's disease (40) and AIDS (41–43). Finally, our biochemical data also suggest the possibility that anticholinergic medication may actually aggravate the symptoms and clinical course of fatal hyperthermia syndrome.

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Parents' Awareness of Children's Suicide Attempts

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In independent psychiatric interviews with 175 children and their mothers, either the mother or the child reported that 13 (7%) of the children had made a suicide attempt. Eight of the 13 children reported attempts that were not reported by their mothers.

(Am J Psychiatry 1990; 147:1364–1366)

S uicide is the third leading cause of death among adolescents; only accidents and homicide cause more deaths in this age group. The suicide rate for 15- to 24-year-olds more than doubled in the past 30 years (1). A history of previous attempts has been associated with completed suicides (1).

Information on the history of suicidal behavior can be useful for identifying persons at risk. Historically, clinicians have depended on parents to identify psychiatric symptoms in their children. More recent studies, however, show that parents may underreport the degree and nature of their children's psychiatric symptoms. These findings, reported independently by several investigators, raise questions about the primary use of parents as informants about psychiatric disorders in their children (2).

In this paper we will present data from interviews with children and their mothers on the history of suicide attempts in the children. Our major finding is that more than half the mothers of adolescents who reported that they had made a suicide attempt did not know about their child's suicide attempt.

METHOD

The children in this study were a subset of 220 children at high or low risk for psychiatric disorder by virtue of the presence or absence of major depression in their parents. Information about the child from direct interviews with the mother about the child and interviews with the child directly were available for 175 of these children, 81 boys and 94 girls, who make up the study group for this report. The children were 6 to 23 years old at initial interview. Details of the method are presented elsewhere (3).

The assessment instruments for each child included the Children's Global Assessment Scale (4) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiology Version (KIDDIE-SADS-E) (5). The Children's Global Assessment Scale, an adaptation of the Global Assessment Scale for adults, is a unidimensional rating scale for evaluating social and psychological functioning during a specific time period on a scale from 1 to 100. Scores above 70 indicate good functioning. The KIDDIE-SADS-E probes for the presence or absence of suicidal behavior and/or ideation, both currently and in the past. Intentionality is scored on a 4-point scale ranging from 1 (low intent) to 4 (serious intent).

The child and the child's mother were interviewed separately with the KIDDIE-SADS-E. A child psychiatrist, blind to parental diagnosis, used all available information to make a best estimate *DSM-III* diagnosis of the child (6). The kappa coefficient, an index of

TABLE 1. Characteristics of 175 Children Who Did or Did Not Attempt Suicide and Agreement Between Mothers and Children on Whether the Attempt Had Occurred

Group	Number of Boys	Number of Girls	Age at First Suicide Attempt (years)	Mean Children's Global Assessment Scale Score	Mean Number of Suicide Attempts	Number of Mothers Who Had Made Suicide Attempts
Children who did not attempt suicide	78	84	—	69.3	—	13
Children who did attempt suicide						
Mother and child agreed that suicide attempt had been made	2	2	17.2	47.2	1.2	1
Mother and child disagreed on whether suicide attempt had been made	1	8	14.0	46.7	2.8	1

chance-corrected agreement (7), was calculated to assess agreement between mother and child on report of suicide attempts, and McNemar's chi-square was calculated to determine whether rates of suicide attempts reported by mother and child differed significantly (7).

RESULTS

At least one lifetime suicide attempt was reported by either the mother or the child for 13 (7%) of the 175 children, three boys and 10 girls. Two of the mothers had two children each who had made suicide attempts. In both cases the mother reported the suicide attempt of one child but not of the other child. Because the interviews of the mother about the child were conducted separately for each child and the interviewer was blind to information obtained from the child, no explanation for this discrepancy was reported.

Agreement between mother and child on the child's suicide attempt was fair (kappa=0.45). Twelve children reported suicide attempts. Mothers reported that five of the children had made suicide attempts. There was agreement between mother and child for four of the children. Eight of the 13 children who attempted suicide, therefore, reported attempts not reported by the mother, and one mother reported an attempt not reported by the child. A significant association was found between informants (mother versus child reports of suicide attempts) (McNemar's χ^2=4.00, df=1, p<0.05). The most frequent methods of attempt were drug ingestion and wrist cutting. Eleven of the 13 children who had attempted suicide had at least one parent who was depressed.

The four children whose mothers agreed with them about their suicide attempts were compared with the nine children whose mothers did not to determine predictors of agreement (see table 1). The ratio of girls to boys was higher among the children whose mothers disagreed about suicide attempts than among those whose mothers agreed (see table 1). The children

whose mothers did not agree about the suicide attempt reported a lower mean age at the time of the first attempt and twice the mean number of attempts as did the children whose mothers did agree about the suicide attempt (see table 1). Four of the mothers who disagreed with their children's reports of suicide were separated or divorced from the child's father; none of the mothers who agreed with their children's reports of suicide were separated or divorced. The current marital status of the mother did not distinguish the agreement group from the disagreement group. The rate of suicide among the mothers who agreed with their children's reports of suicide was twice as high as the rate among mothers who did not agree with their children's reports and three times as high as the rate among mothers of children who did not attempt suicide (see table 1).

The children who did not attempt suicide, those who did and whose mothers agreed, and those who did and whose mothers disagreed differed in Children's Global Assessment Scale scores and rates of psychiatric disorders. The children who had not attempted suicide were the least impaired according to their Children's Global Assessment Scale scores (see table 1) and had the least number of psychiatric disorders. The two groups of children who had attempted suicide were seriously impaired and had low Children's Global Assessment Scale scores that did not differ appreciably (see table 1). All of the children who had attempted suicide were diagnosed as having major depression at some point in their lives. The most common comorbid diagnoses were conduct and anxiety disorders and substance abuse. Five of the nine children whose mothers disagreed about the suicide attempt had a diagnosis of substance abuse, compared with one of the four children whose mothers agreed about the attempt and 16 (10%) of the 162 children who did not attempt suicide.

The children whose mothers disagreed about the suicide attempt were equally distributed along the 4-point scale of intentionality. Three of the four adolescents in

the group whose mothers agreed about the suicide scored in the definite intent range, and one scored in the minimal intent range. Mothers reported lower scores on intentionality than did their children. The following cases illustrate the nature of the attempts.

CASE REPORTS

Case 1. Karen, an 18-year-old girl whose parents were divorced, reported a major depression at the age of 17, following a therapeutic abortion. Karen's guilt over the abortion resulted in her taking an overdose of pain pills, which left her lethargic. She went to an emergency room and was released the same day. She described the attempt as serious in intent. Although Karen's mother reported her daughter's depression and suicidal ideation, she did not report the suicide attempt.

Case 2. Jane, who was 16 years at the time of interview, reported three major depressive episodes. The first occurred when she was 7 years old after her parents divorced; the second at age 11, when her mother remarried; and the third at age 14 after a miscarriage. During this last episode she impulsively cut her wrists at school but concealed the wound. Her mother was unaware of the cuts or the suicide attempts.

Case 3. Alice was 17 years old at the time of interview and lived with her parents. She reported having experienced a major depression when she was 14. She was impaired and missed school during this time. She cut her wrists on two separate occasions but wore long sleeves so that her mother would not notice the bandaged cuts. She described the cut on the first occasion as deep and painful, and she described her intent as serious. She repeatedly asked her parents for someone to talk to, but her request was denied. Alice's mother during the interview denied any symptoms of depression in her daughter.

DISCUSSION

There are two major findings of this study. First, the majority of mothers in this study group whose children reported suicide attempts were unaware of these sui-

cide attempts. Second, compared with the mothers and children who agreed with each other that a suicide attempt had been made, the mothers and children who did not agree that an attempt had been made were characterized by a younger age in the child at the first attempt, a greater mean number of lifetime attempts by the child, more serious intentionality in the child, separation or divorce from the child's father, and a higher rate of attempted suicide in the mothers.

These findings on suicide attempts are consistent with accumulating data suggesting that parents are often unaware of or underreport psychiatric disorders in their children (2). These findings can now be extended to suicide attempts. Suicidal behavior can be added to the list of other concealed behavior of adolescents (i.e., drug and alcohol use). This has obvious implications for determining accurate prevalence rates of suicidal behavior and assessing suicidal potential in an individual adolescent. Further studies using larger samples are required to confirm and expand these preliminary findings.

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Exclusion of the Tyrosine Hydroxylase Gene in 14 Panic Disorder Pedigrees

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The authors examined the linkage between the tyrosine hydroxylase locus and panic disorder in 14 multiplex pedigrees and excluded tyrosine hydroxylase as a cause of the disorder in these pedigrees.
(Am J Psychiatry 1990; 147:1367–1369)

Tyrosine hydroxylase is an important enzyme that may be relevant to psychiatric disorders because it is the rate-limiting enzyme in the synthesis of catecholamines (1). It converts tyrosine to 3,4-dihydroxyphenylalanine (dopa) and subsequently to dopamine, norepinephrine, and epinephrine. A role for the catecholamines has been proposed in the pathogenesis of affective, anxiety, and psychotic disorders.

A mutation in a gene coding a rate-limiting enzyme would most likely result in a lower level of a neurotransmitter. Although lower postsynaptic levels of norepinephrine would be expected to decrease anxiety, lower stimulation of presynaptic α_2 autoreceptors is associated with greater anxiety and could contribute to the state of sympathetic dysregulation that has been proposed in panic disorder (2). Moreover, alternative splicing of tyrosine hydroxylase mRNA (3) provides a mechanism by which a mutation to a gene encoding a widespread neurotransmitter could lead to a limited syndrome such as panic disorder.

Genetic linkage tests candidate genes by phenotyping pedigrees with the DNA encoding the gene (4). If affected family members share neither allele at the gene locus, the candidate gene can be excluded in that pedigree. Conversely, if the candidate gene is the cause of the disorder, the absence of recombination between disease and marker would provide evidence of linkage. We have used this strategy to study the tyrosine hydroxylase gene in panic disorder.

METHOD

Families were identified through patients seeking treatment at our anxiety disorders clinic. Twelve families with at least three affected relatives by family history, spanning at least two generations, were included, and two more were referred by practitioners outside of the university.

Twelve families were interviewed by one of us (R.R.C.) and two were interviewed by fourth-year psychiatry residents using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) or the Structured Clinical Interview for DSM-III (SCID) supplemented by a narrative summary. Written informed consent was obtained from all subjects before proceeding. Diagnoses were made according to *DSM-III* by clinicians who had no knowledge of the genotype data. The details of the diagnostic process are described elsewhere (5). Diagnoses of probable panic disorder were made when subjects had attacks with insufficient criterion symptoms or had too few attacks for a *DSM-III* diagnosis of panic disorder. Further, the panic attacks had to be chronologically independent of affective disorder to qualify for a diagnosis of anxiety disorder.

DNA was extracted from buffy coat preparations by phenol/chloroform extraction, digested with the restriction enzyme Dra I, electrophoresed in 0.8% agarose gels, and transferred to charged nylon membranes. A 1.5-kilobase cDNA probe for the human tyrosine hydroxylase gene pCB-05 (6) was labeled with $[\alpha^{-32}P]dCTP$ by the random primer method and hybridized to the blots. Blots were washed at high-stringency (0.1X standard saline citrate, 0.1% sodium dodecyl sulfate) and exposed to X-ray film with image intensifier screens to produce autoradiographs.

The tyrosine hydroxylase probe detects a 15-kilobase and a 12-kilobase band restriction fragment length polymorphism in Dra I digests, with allele frequencies of 0.24 and 0.76, respectively (6). Another probe for the tyrosine hydroxylase locus, pHGTH4 (from the American Type Culture Collection, Bethesda, Md.) was used, but complete linkage disequilibrium between the two made haplotyping uninformative. The autoradiographs were read blind to the subjects' clinical diagnoses.

TABLE 1. Lod Scores for Linkage Between Panic Disorder and Tyrosine Hydroxylase in 14 Pedigrees

Recombination Fraction	Lod Score
0.00	−4.55
0.05	−2.17
0.10	−1.24
0.20	−0.37
0.30	−0.05
0.50	0.00

Linkage analyses were conducted by using the LIPED program (1988 version for the IBM PC/AT) (7). The genetic model assumed both definite and probable panic disorder to be the result of a dominant allele with a frequency of 0.014 and incomplete penetrance. Penetrance began at age 10 and reached a maximum of 0.8 by age 40 in women. Penetrance in men was half that of women at each respective age. This model is based on a segregation analysis of Iowa pedigrees with the best-fitting parameters, modified slightly for consistency with epidemiologic data on panic disorder (8). The genetic model also assumed the absence of phenocopies.

RESULTS

One hundred forty-five individuals in 14 pedigrees were phenotyped and entered into the linkage analysis. The 14 probands were 11 females and three males with a mean age of 34.7 years (range=14–55 years) and a mean age at onset of 23.4 years (range=8–35 years). All had DSM-III panic disorder or agoraphobia with panic attacks. The mean±SD age of the 145 individuals was 45.1±15.8 years; 87 were female and 58 were male. Sixty-two of the 145 individuals had panic disorder or agoraphobia; five had probable and 14 had definite panic disorder, and four had probable and 39 had definite agoraphobia.

The statistic used to measure linkage is the lod score; a lod score greater than 3.0 indicates that the pedigrees support linkage over the null hypothesis at a statistically significant level, and a lod score less than −2.0 indicates that they support the null hypothesis at a statistically significant level and linkage can be excluded. Thus, a locus for panic disorder was excluded up to 5 centimorgans from the tyrosine hydroxylase locus by virtue of lod scores of less than −2.0 at recombination fraction of 0.05 (see table 1). Notably, in two of the pedigrees recombination between disease and marker occurred between two affected relatives. In one case it occurred between the proband and a great-aunt and in the other between two half-siblings. Three pedigrees contributed positive lod scores at the zero recombination fraction (0.86, 0.23, and 0.11). Therefore, the material was tested for genetic heterogeneity with the b test (9); no evidence of heterogeneity was found (b test statistic=0.19).

Since the genetics of panic disorder are unknown, it is important to analyze the data according to a number of genetic models to ensure that the results are not an artifact of the model used. Additional analyses allowed the disease allele penetrance to range from 0.50 to 0.99 and the region excluded ranged from 2 to 10 centimorgans, respectively. When only definite panic disorder and agoraphobia were counted as affected and probable cases were counted as unaffected, the lod scores were less than −1 over 5 centimorgans of genome, although the tyrosine hydroxylase locus was not formally excluded. A similar result was obtained when the penetrance was set at 0.01. This analysis forces the lod score to be based only on affected pedigree members; therefore, it is not sensitive to assumptions about penetrance.

DISCUSSION

If affected relatives share no allele at the candidate gene locus, the candidate is excluded from the pathogenesis of the disease in that family. Thus, tyrosine hydroxylase has been excluded as a cause of panic disorder in our 14 pedigrees. Although this is a powerful research method in theory, some limitations of the method as it relates to psychiatric disorders need to be considered.

Exclusion mapping is sensitive to genetic heterogeneity because the underlying assumption is that one recombinant excludes the candidate gene. If genes at more than one locus produce the disease, the candidate gene will be falsely excluded. If heterogeneity exists, the fact that recombination will not occur in the linked pedigrees will make it easier to detect statistically by generating larger positive lod scores in these pedigrees. Only one of our pedigrees was suggestive of linkage (lod score=0.86), but this did not result in statistical evidence of heterogeneity.

Diagnostic uncertainty is another source of false exclusion because unaffected relatives may be incorrectly classified as affected. Both pairs of obligate recombinants in our pedigrees occurred between relatives with definite diagnoses, making misclassification unlikely.

A third source of false exclusion is incomplete penetrance. If an unaffected parent were a carrier of the disease allele, then affected relatives would inherit different disease alleles and thus not be obliged to share an allele at the candidate gene locus. Thus, the family history of every person marrying into the pedigree is important, and sibships must be excluded when there is evidence of bilateral inheritance.

If enough obligate recombinants were present to exclude the candidate gene, the results would be free of assumptions about the mode of inheritance of the disease. Otherwise, a different genetic model needs to be examined to ensure that the conclusions are not model dependent. The fact that all of the models we examined gave negative lod scores increases confidence that the conclusions are supported by the data.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

CONCEPTS AND ISSUES

The Second Medical Revolution: From Biomedicine to Info-medicine, by Laurence Foss and Kenneth Rothenberg. Boston, New Science Library (Shambhala), 1987, 328 pp., $29.95.

To the extent that medicine has emerged from folk wisdom, superstition, and morality into the enlightenment of science, it has undergone revolutionary changes. This "first revolution" continues, forming the basis for our dominant contemporary medical model. As we have lived with the modern biomedical model of disease, we have become progressively aware of its limitations, particularly its failure adequately to incorporate the multitude of variables operating in the complex human biology system.

In the 13 years since George Engel, who wrote the foreword to this book, published his classic article proposing the biopsychosocial model as a new model of disease (1), we have seen the term "biopsychosocial" increasingly misunderstood and misused. Engel's model was an outgrowth of general systems theory and aimed to describe the interaction of variables that cause disease. Now it is often separated into ingredients as if to be used in a recipe—a dash of the biological, a pinch of the psychological, and a smidgen of the social—frustrating the original emphasis on interactions.

The changes in thinking wrought by quantum mechanics, irreversible thermodynamics, self-organizing systems, and cybernetics may seem remote to our concerns as physicians and psychiatrists, but this is not the case. The authors of this book successfully make use of these scientific concepts to formulate a new way of viewing disease, which they refer to as the "second medical revolution," and, in so doing, make postmodern science relevant to medicine and psychiatry.

The first of the four parts of the book contains an orderly, clear, and accurate review of the development of the modern medical model. The second part, Prelude to Revolt, explores the limitations of the biomedical model, including its lack of adequate consideration of psychosocial matters. The authors then proceed to a critical analysis of the various compromises with the biomedical paradigm. Engel's biopsychosocial model and its relation to general systems theory is respectfully dealt with as one such compromise serving a transitional role toward a more comprehensive model, which Foss and Rothenberg propose in a later section. Engel agrees with this view in his foreword. The last chapter in this section explores the role of psychosocial factors in disease causation and the influence of the hard science view. Recent work in psychoneuroimmunology is used to bridge the so-called soft and hard views.

The third part moves the reader through the steps necessary to understand the new model, which the authors call the infomedical model. They explore cybernetics and self-organizing systems in terms of human biology in a very clear manner that should be enlightening to those who have not been exposed to this type of logic. By the end of this part of the book, the authors have successfully explained their

model. The reader, I think, will be left with a sense of having been bound by simple notions of causality that no longer are comfortable but that are not easy to abandon. The term "infomedical" recognizes the person (patient) as being central to the disease process, functioning as "an information processing system with multilevel programs processing multilevel messages, whose interaction determines the health and well being of the system" (p. 201). Information is used in a much broader sense than cognitive facts; it includes the inputs of subcellular functions up through the influence of the ecosystem. In other words, the person is the medium through which variables are organized, mediated, and expressed. In the case of dysfunction the person is a patient and the disease is the expression of the dysfunction. This model is a drastic, much-needed move away from reductionist approaches to understanding disease. When one accepts the modern concepts of self-organizing systems, interactionism, and mutual causality, the model is not only sensible but enlightening.

The meaning of the proposed model, including the potential for mental events to cause disease, is explored in the last part of the book. These final chapters are interesting but not so strong, clear, or convincing as the earlier parts of the book. Illustrating how the model operates in disease causation is easier than formulating a general approach to medicine and care based on the model. In this regard, Engel may not have given enough credit to the capacity of his biopsychosocial model to influence what happens between physician and patient.

The authors of this important book are not physicians. Foss has a doctorate in philosophy and writes on the philosophy of science. Rothenberg has a doctorate in education and teaches in interdisciplinary studies. They came to focus on medicine as "the most interesting avenue for exploring" a postmodern world view of science. Being professionally distant from medicine has not diminished their trenchant analysis of the biomedical model; nor has it encumbered their creative efforts to produce a new model. However, it may account for their difficulty in applying their new model.

Psychiatry has historically been attuned to the interaction of variables in the origin and maintenance of dysfunction. With the rapid growth of knowledge in the area of brain function we may, at times, seem to be headed down a reductionist road. This book will be appreciated by and useful to those who are looking for a means of understanding and articulating an interacting-variables model of disease. In this regard, many of us need to articulate this not just for ourselves but for our patients, our students, and our residents, all of whom show evidence of being befuddled by the competing theories of mental dysfunction to which they are exposed.

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Body Experience: The Subjective Dimension of Psyche and Soma Contributions to Psychosomatic Medicine, *edited by E. Brähler. New York, Springer-Verlag New York, 1988, 244 pp., $55.90.*

The editor of this translated volume believes that "the individual's experience of his or her own body, which is always a subjective experience, is still not taken seriously enough," and he attempts to persuade practitioners to integrate the "body" into current medical and psychological therapy. Yet neither he nor the 21 contributing authors make clear enough the clinical rationale for such integration. Add to this the fact that vital terms such as "psychosomatic" and "psychoanalytic approach" remain unexplained, and the result is a collection that never quite comes into focus.

The book is organized into four sections with interesting headings: The Significance of the Body Experience, The Body Experience in Therapy, Sex-Specific Body Experience, and Measuring Body Experience and Body Complaints. The sections comprise 18 chapters among which there is often considerable redundancy, however. Although the text has been translated (less than gracefully in many places), the numerous references are in German.

Disappointingly, most of the material has not progressed much past the 1950s and 1960s, when the central focus of "psychosomatic" inquiry was whether particular psychological features determined which organ system would be afflicted. The notion that psychological distress can emanate from somatic illness rather than cause or predispose to it is largely underemphasized by the authors.

The chapters tend to resemble superficial (and often dated) reviews; there is generally little attempt to synthesize or critically assess previous work or to trace the development of ideas about the relationship between somatic and psychic functions. Rarely are arguments put forth, nor are hypotheses generated. An example of the type of dogmatic and antiquated statement made throughout is the following: "In the case of a disturbed body image, the defective body schema, there cannot be a reliably cathexed feeling of self furnished with neutralized energy. The quality of personal hygiene and the way in which toilet training was handled are probably pathogenic here" (p. 124).

All this leads one to wonder just where *is* the individual in this book? It seems that the word "subjective" in the title really refers to an objectification of the inner experience. Consequently, the individual does not come alive. How can such a sterile vision of phenomenology play a role in psychotherapy when a critical element of treatment may be the therapist's empathic idea of the patient and the communication of possibilities to him or her?

Brief case vignettes are presented to demonstrate that psychological and somatic events are linked. Small epidemiologic studies serve to document, in checklist fashion, the types of body sensations and emotional responses associated with conditions such as prostatitis, vaginal discharge, and infertility. The next clinical step, which would entail predicting or demonstrating that these variables correspond to treatment outcome or course of illness, is not taken. The authors, on the whole, do not control their studies, define variables or outcome measures, or describe subject recruitment and selection. Further, they do not offer alternative explanations for findings.

Several editorial features of the book make it difficult to read, and its price makes it difficult to buy. The book's print is densely crowded on the page, there are many typographical errors, and occasional words have eluded the translator.

The preponderance of references *auf Deutsch* render them inaccessible to the average reader.

The modern psychotherapist and internist will, I feel, find little of clinical relevance here. In my view, this volume may be helpful to scholars, who might use it as an annotated bibliography of classic works in the area of "psychosomatic" medicine.

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Race and Culture in Psychiatry, *by Suman Fernando. London, Croom Helm (New York, Routledge, Chapman & Hall, distributor), 1988, 204 pp., $49.95.*

This brilliant but ultimately flawed book is not a treatise on race or culture or psychiatry. Rather, it is a thoughtful polemic about all three topics in a particular context. The setting is current British society; the author, a consultant psychiatrist at a hospital in Middlesex, is Sri Lankan, erudite, and deeply allied with the victims of racism.

The book's basic arguments are clearly stated. Race may be a biological myth but it is very much a social reality. Ideas about race are very strong in Britain. Since British psychiatry is enmeshed in the larger society, it is pervaded by racist ideas. "Although racial theories are not stated overtly, current psychiatric literature in Britain tends to reflect the racist ethos which is evident in society at large" (p. 34). Copious examples are provided to demonstrate clearly how racial ideas affect research methodology, psychological tests and instruments, diagnosis, therapy, and prognosis. Psychiatry conceals, defends, and maintains racism by culturizing it: "Injustices and disadvantages suffered by black and ethnic minorities are attributed to their culture which causes *them* to distort illness patterns (for example by somatising psychological symptoms), make unreasonable demands (for instance by exaggerating symptoms or not expressing them) or not benefit from treatment (by not speaking a European language, by communicating in ways that psychiatry sees as 'primitive,' etc.)" (p. 130). Cultural psychiatrists are the worst offenders because they give the false appearance of being understanding and culturally sensitive.

Fernando presents a blueprint for change. He calls for the formation of a "reform group" within the Royal College of Psychiatrists that would directly confront racial and cultural issues. He wants a Mental Health Agency to be established, in parallel with the National Health Service, that would be amenable to the influences of consumers. Grant-giving organizations and ethical committees "should ensure that all research projects that involve black and ethnic minorities take on the racial dimension in terms of its effect on researchers' attitudes and misconceptions determined by the racist context of society, and the fact of racism as a major cause of social stress to black people" (p. 174). Each major psychiatric journal should solicit papers on racial and cultural issues in psychiatry, recruit referees who represent the views of ethnic minorities, and "stop publication of papers submitted from South Africa unless they are statements criticizing the system of apartheid psychiatry in that country" (p. 176). Treatable, committed patients should be sent only to hospitals that fulfill a "suitability" criterion that takes into account "the cultural characteristics of the patient, the total environment of the hospital including its staffing structure, and racism in society" (p. 178). Administrators in each mental health district should report on actions taken to ensure

the cultural sensitivity of professional practice and to exclude racist practices.

The author's loathing of racism is evident, and his arguments, in great part, make a lot of sense. However, his intolerance of human imperfection is counterproductive and his condemnations too sweeping. His reasoning has no room for persons of goodwill. Surely, even in Britain, not every white psychiatrist is inevitably either an overt or a covert racist. Surely not every black psychiatrist who fails to be appointed to a desirable position is a victim of racism. Surely not every black professional who succeeds in the psychiatric system becomes an "honorary white" and slips into a racist frame of mind. Surely not every interaction between a white psychiatrist and a black patient (or a black psychiatrist and a white patient) is contaminated by racism.

The information in the book is thought-provoking and sometimes startling. It is undeniable that many racial misperceptions exist in psychiatry and, certainly, no one would argue that these misperceptions need to be rectified. What I find objectionable in the book is the author's relentless reductionism. For Fernando every issue is clearly black and white, and every white psychiatrist is guilty until proven innocent. The social situation in Britain may be grim, but even in countries such as South Africa one can find psychiatrists of clear mind and goodwill who are able to transcend racism. Although I heartily endorse many of Fernando's sentiments and appreciate his scholarship, his siege mentality and apparent unwillingness to extend even a modicum of trust to any colleague who is not dark-skinned detracts from the book.

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Homelessness in the United States, vol. I: State Surveys, *edited by Jamshid A. Momeni. Westport, Conn., Greenwood Press, 1989, 258 pp., $49.95.*

This book is the first of two volumes of *Homelessness in the United States* edited by Dr. Momeni, an associate professor in the Graduate School of Arts and Sciences at Howard University. According to the editor, the promised second volume will cover such issues as "homelessness and drug problems, housing, and economic survival strategies." Two-thirds of the 27 contributors to the first volume are sociologists; none is a psychiatrist or psychologist. The perspective of the book is, not surprisingly, strongly sociological.

This volume consists of survey material from 15 states on the history, numbers, and response to the problem of homelessness in that state. Dr. Momeni is to be commended for attempting to collect empirical data in a research area where opinions far outstrip facts. The surveys also demonstrate both the multiplicity of subgroups that make up the homeless and the variability of these subgroups from geographic area to area. Since the majority of the data on homelessness has to date come from large urban areas, the data from more rural states (e.g., Tennessee and Alabama) are especially useful. The importance of a declining supply of low-income housing in exacerbating the homelessness crisis is also highlighted in most of the surveys, which is not surprising because the editor has published two previous books on housing (1, 2).

The limitations of this volume, however, are substantial. The state surveys are not comparable either in terms of when they were carried out or in terms of methodology (e.g., definitions of homelessness). Dr. Momeni and many of the con-

tributors to this book believe that serious mental illness and deinstitutionalization are not very important contributors to the homelessness problem. In his preface, Dr. Momeni asserts, "The data in several chapters in this volume show that on the average only about 25 to 30 percent of the homeless suffer varying degrees of mental illness (in some cases a consequence of homelessness itself). The remaining 75 percent are perfectly normal, average people." In fact, there was almost no assessment of mental illness in the surveys other than self-reports of past psychiatric hospitalizations, which varied widely, are known to be subject to serious underreporting, and omit many of the young people with chronic mental illness who have never been hospitalized. Surveys of the homeless carried out by mental health professionals have consistently found one-fourth to one-third of the urban homeless to have or have had serious mental illnesses (schizophrenia or bipolar disorder). Another one-third have substantial alcohol or drug abuse problems. It would certainly simplify planning and programs for the homeless if 75% were "perfectly normal, average people," but that unfortunately is not the case.

Despite this shortcoming, because of the primary data that the editor has collected in one place, this volume will be useful to those with a special interest in the homeless. It is hoped that volume II will include a more detailed analysis of these data.

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RESEARCH METHODS

Studies of Psychosocial Risk: The Power of Longitudinal Data, *edited by Michael Rutter. New York, Cambridge University Press, 1989, 392 pp., $59.50.*

The time-honored clinical method for exploring developmental antecedents is the retrospective inquiry. There are few other convenient sources of information for most individuals.

What works well for the clinician does not for the researcher. Although many major insights have come from retrospective study, there are too many factors preventing accurate recall for rigorous scientific proof. This realization led to the adoption of longitudinal techniques quite early in the late 1920s, with growth studies and some early follow-up studies of problem children. In the last 20 years such studies have come into their own in psychiatry as research that was commenced much earlier has started to bear full fruit. These are studies for an affluent and well-developed research world; they are expensive and require the capacity to delay gratification to the longer-term.

They also show another characteristic of affluence: they lend themselves to scientific exchange in a research network. This book originates from a 1987 workshop of a network for longitudinal studies set up by the European Science Foundation. The list of contributors reads like a guided tour of

major European longitudinal studies, with, among others, the Maudsley represented by Michael Rutter; Cambridge by Hinde (development) and Farrington (delinquency); the Medical Research Council's British National Survey of Health and Development by Wadsworth; Stockholm by Magnusson and Bergman; and delinquency in Finland by Pulkkinen. There is a leavening from elsewhere, including Fergusson and Horwood from New Zealand and Lee Robins from St. Louis, whose long-term follow-up of children still stands as a classic model. The European origin of this book should provide something new for U.S. readers.

Despite the workshop origin and the parentage in major studies, this reads like a book, not a collection of conference papers. The emphasis is on issues of method and designs for studying particular kinds of causes, theory, and major themes rather than detailed study results that have been published elsewhere. As Rutter points out, longitudinal studies are particularly useful for unraveling multiple causes and complex causative chains where any cause is modified by many subsequent factors. For instance, the effects on children of the breakup of the home depend on whether parental discord has preceded it and on the quality of substitute parenting. Chapters look in detail at designs, statistical approaches to analysis, applications to specific situations such as child development and delinquency, biological risk factors, school experiences, normative events such as birth of a sibling, and intergenerational studies of children studied from birth who themselves become adult parents.

The chapter authors speak with authority. Most of them write well and clearly, although they make no attempt to oversimplify complex issues. This book is meant for researchers, and it ranks as essential reading for those who are conducting longitudinal studies or would like to undertake them.

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The Instruments of Psychiatric Research, edited by Chris Thompson. New York, John Wiley & Sons, 1989, 352 pp., $74.00.

In his introduction, Professor Thompson says that one aim of this review of diagnostic interviews and rating scales for use in psychiatric research is "to provide an inventory of the available instruments, at least the most prominent ones." He implies that by studying this book readers should be able to discern which scale or scales are best suited to their research protocols and patient populations. This is possible only if readers' interests match the book's strengths, because some chapters are likely to be more helpful than others. For example, Dr. Thompson's chapter on rating scales for affective disorders is quite thorough, but the chapters on scales for neurotic symptoms and personality disorders discuss the instruments available in far less breadth and depth.

The introduction contains some discussion of the theoretical basis of rating scales and the statistics used to describe and compare them. Several important concepts, however, are not discussed. There is an excellent discussion of sensitivity, specificity, predictive value, and receiver-operating characteristic curves in the chapter by Bridges and Goldberg on neurotic symptoms, but this discussion belongs in the introduction. There should be some discussion in the introduction of the intraclass correlation coefficient, which is described in a footnote by Angold, as well as a comparison of this statistic

with correlation coefficients for assessing reliability. Discussion of measures of agreement on categorical variables, such as kappa and chi-square, would also be appropriate in the introduction.

The chapter on structured diagnostic interviews is a good review of some of the commonly used instruments, and the 11 chapters on rating scales for different symptoms or syndromes cover a wide range of psychiatric illness. The chapters differ in the depth and breadth of their coverage; some authors tend to concentrate on the scales developed by themselves or their colleagues.

I am not sure that I would know enough after reading a chapter in this book to select from among the scales discussed in that chapter. I would have found a table or two in each chapter comparing the scales helpful. These tables could include information on whether each scale was self-rated or observer-rated, whether the results obtained by using each scale had been replicated by independent investigators, for which clinical populations the scale would be appropriate or inappropriate, and the length of time it takes to administer or complete each scale. This important information is not always easy to find in the chapters as they are written.

This book is a useful resource for those wanting an overview of rating scales for some clinical populations and for some symptoms and syndromes. I would not ask our library to order the book, however, because its cost is greater than its usefulness.

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COMPUTERS

Computer-Intensive Methods for Testing Hypotheses: An Introduction, by Eric W. Noreen. New York, Wiley-Interscience (John Wiley & Sons), 1989, 226 pp., $24.95 (paper).

The possibilities of innovation in psychiatric research can only be enhanced by the introduction of alternative methods of testing hypotheses. Basically, a hypothesis test asks how likely an observed event (e.g., a mean difference) would occur if the conditions of a study were replicated an infinite number of times. Although computers cannot replicate things an infinite number of times, they can quickly generate several hundred replications and thus estimate the likelihood of an event. These estimation methods are becoming fashionable. In principle, the computer-intensive methods outlined in this book allow some hypotheses to be tested that deal with statistical indexes of the researcher's own fabrication. Therefore, novel or clever research measures can be generated tapping an effect or gauging a relationship and subsequently tested. One need no longer be constrained to such techniques as correlation coefficients and tests for differences in means.

It is unfortunate that this book does not go into more detail, offer guidelines, or present more examples of how this freeing effect might be used by researchers in psychiatry. Only a few examples are given using a novel circumstance, and none of these deals with a topic that might be related to psychiatry. Although the methods are still useful, it would have been worthwhile to see some more interesting applications.

The author makes a distinction between this book and a "cookbook," suggesting that this book provides an under-

standing of the methods. However, fewer than 100 pages are devoted to text, and more than 100 pages are devoted to listings of computer programs that can be typed into a computer. Although these programs are readable by someone with an intermediate level of programming expertise, I do not think that they are the best way to provide an understanding of the methods. The technical appendixes cover important topics but require a reasonably sophisticated background in statistical theory.

From a technical standpoint, this book looks reasonable. I replicated some of the techniques, and my results corresponded quite nicely to those of the book. There were a few questionable parts in the text, however. For instance, the book credits a 1963 paper by G.A. Barnard as introducing the Monte Carlo method of assessing the significance of a test statistic, but that method had been used before 1963 (1, 2). Elsewhere, the wording is not quite accurate. For example, on page 63 a particular area under a curve is called the sampling distribution. In addition, there are some apparent typographical errors that might cause confusion. For example, on page 72, referring to a table with alpha levels of 0.05 the text refers to them as 0.10; judging from the actual numbers it appears that the text is incorrect.

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UNIX: The Minimal Manual, by Jim Moore. Rockville, Md., Computer Science Press (New York, W.H. Freeman and Co., distributor), 1988, 238 pp., $17.95.

More and more computer systems using the UNIX operating system are being installed in academic institutions. Although this operating system has for many years been considered far too complex and advanced for the new or inexperienced user, many people now face the task of using this operating system as new computer systems that use UNIX become available on campuses and in other highly technical areas of the community. I recently found myself confronted with administering a network of UNIX-based work stations and felt completely overwhelmed by the deluge of manuals and operating instructions that came with them. Although I had investigated the topic before, I had not found a simple and concise introduction to the use of this marvelously complex and rich operating system until I came across UNIX: The Minimal Manual by Jim Moore. This book proved to be an excellent first step on the road to understanding and managing UNIX.

This book is a marvelous introduction to the file management and word processing capabilities in nearly every flavor of UNIX in existence. Included is a description of how to create files and directories, the editing and printing subroutines that are used, and how to use the basic and intermediate features of UNIX Mail. Since at this time UNIX, as an operating system, is used mainly as an interface in which to program, the use of the file-editing capabilities is the first important lesson for any new user. Mr. Moore starts his tutorial of UNIX with the fundamentals—how to log in and

out of a UNIX system. From there he takes us on a tour of directory management and then to the heart of UNIX, the vi and ed editors. From this point we are taken through the commands for editing a document and shown how to format the document for attractive output (the nroff and troff print commands and the -me and the -ms macro command languages). There is an extended explanation of the different bibliographic systems that are available to the user, along with some "quick fix" emergency measures for retrieving deleted files and other mistakes. Mr. Moore ends his manual with a comprehensive list of commands and their syntax. He even includes the more advanced techniques of using "aliases" to make complicated command strings easy.

There is an increase in placement of UNIX-based computer systems tied to the already complicated medical and scientific instrumentation available today (examples include implementation of UNIX on IBM PC RT, Apple Macintosh II, Sun, Apollo, and Silicon Graphics work stations and instrumentation). It is refreshing to find a simple, no-nonsense manual for UNIX. Mr. Moore has shown us that just as you do not need to be a plumber to take a shower you do not need a degree in computer science to use an advanced computer system. You just have to read the manual.

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GENETICS

Molecular Genetics in Medicine: Progress in Medical Genetics, vol. 7, edited by Barton Childs, Neil A. Holtzman, Haig H. Kazazian, Jr., and David L. Valle. New York, Elsevier, 1988, 200 pp., $47.75.

As has been vividly displayed by the recent success in the mapping, cloning, and characterization of the gene for cystic fibrosis (1), the age of molecular genetic medicine is upon us. Since 1983, with the mapping by linkage analysis of Huntington's disease, nature has yielded her secret of the location on the human genome of the gene responsible for each of an increasing number of classic human Mendelian disorders. Many are expecting that in the next 10 years we will see a similar pattern of successes with the so-called complex phenotypes (disorders which, although they "run in families," do not have a classic Mendelian pattern of transmission), including the major psychiatric disorders of schizophrenia, bipolar and unipolar affective illness, Alzheimer's disease, anxiety disorders, and alcoholism. Others are skeptical and point to such problems as possible polygenic transmission (many genes in any given family influencing vulnerability to a disorder), genetic heterogeneity (different major genes in different families influencing vulnerability for the same apparent syndrome), uncertain definitions of illness, and confounding environmental risk factors. Although the eventual impact of molecular genetics on the world of psychiatric research and practice is uncertain, there is little reasonable doubt that its importance will continue to grow.

How, then, do psychiatrists unfamiliar with this field and its initially bewildering vocabulary obtain an introduction to the world of restriction mapping and chromosome libraries, of Southern blots and lod scores? How do research workers in mental health, broadly familiar with the field, keep pace with the advances of this rapidly moving field?

These are the questions I had in mind as I read this book,

edited by four eminent human geneticists from Johns Hopkins. The book, published in 1988 but almost certainly written in 1986–1987, consists of 10 chapters. The editors have chosen the contributing authors well, and many are among the best-known workers at the interface of molecular genetics and medicine. Unfortunately for the interested but uninitiated, however, this book was not written for the novice. Although it is true that several of the chapters (most notably, the introduction and a particularly interesting chapter entitled "Recombinant DNA Analysis of Multifactorial Disease") are written for a nontechnical audience, the authors of the core chapters of the book, which deal with recombinant DNA methods, clinical application of gene mapping, prenatal diagnosis, and gene therapy, have written as if they were reviewing their area for colleagues or students rather than for newcomers to the field. The instruction of complete newcomers, who might be mildly anxious about their entry into this strange "high tech" world, does not seem to have been uppermost in the authors' minds. Rather, the chapters seem to be oriented for a first-year graduate student or genetics fellow who already has at least a passing familiarity with the key concepts. This approach is particularly evident in the use of illustrations, which are often inadequately integrated into the text. If the goal is to make molecular genetics nonthreatening to the newcomer, this book suffers by comparison with the excellent but now increasingly outdated work of Watson et al. (2). The explanations of linkage analysis do not approach the clarity achieved by Suarez and Cox in a recent pair of articles aimed for a psychiatric audience (3, 4). Furthermore, there is no glossary in this book, and terms such as "allele," "exon," "intron," "hybridized" and "intragenic" are used without definition.

Finally, the book suffers from a common weakness of multiauthored works: repetition. Three different chapters outline the principles of linkage analysis in man, and two review the methodology of Southern blotting. Although repetition can be helpful, in this context the reader would have been better served by an editorial effort to produce one, more thorough explanation of these key concepts rather than the numerous, less adequate ones produced here.

For these reasons, this book will be of most use for those who, although not newcomers to the field of molecular biology, feel a need to refresh and update their knowledge. For such individuals, the book should succeed reasonably well, provided they read it soon, because it will quickly become outdated. Few of the references cited were published after 1986, and the technology in this area is advancing rapidly. For those in the field of mental health, this book is most useful for the insights it provides into the genetics of better understood conditions. Although many may be aware of the problem of allelic heterogeneity (where similar or identical syndromes result from different mutations in the same gene), the magnitude of this phenomenon is strikingly demonstrated by the discussion in chapter three on the genetics of thalassemia. The molecular genetics of this disorder are now almost completely understood, and it has been shown that a similar syndrome can be caused by literally dozens of different mutations. Similarly, genetic heterogeneity (genes at different locations causing the same illness) is currently much discussed in psychiatric genetics. Chapter four provides several clear-cut examples of genetic heterogeneity in well-understood disorders recently revealed by linkage studies.

Those with enough interest to finish this book will, I suspect, be left with a mixture of awe and envy. As a psychiatric researcher whose work increasingly borders on the field

of molecular genetics, I know how the tortoise felt as he watched the hare streak by.

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Genetic Analysis of Complex Traits, Part II: Affective Disorders, edited by John P. Rice, Neil Risch, and Lynn R. Goldin. New York, Alan R. Liss, 1989, 156 pp., no price listed.

This is a compilation of results presented at the fifth annual genetic analysis workshop, held at Chantilly, France, Sept. 2–5, 1987. Data sets (real or simulated) concerning human diseases of genetic etiology are distributed at these annual meetings. At the workshop, participants present results of either theoretical developments that would be useful in analyzing such data sets or actual analyses. By agreeing to work on common data sets, the researchers can compare results of different methods of analysis. These papers also appeared in the journal *Genetic Epidemiology.*

This book is important reading for students of psychiatric genetics. One reason for this is the data sets: the NIMH Collaborative Program on the Psychobiology of Depression—Clinical data set, collected by investigators at five university medical centers and containing families of bipolar probands; the NIMH Family Study, led by Gershon, containing families of probands with bipolar or severe affective disorders; a set of bipolar illness pedigrees informative for X linkage that were reported in different publications; data on human lymphocyte antigen (HLA) typing for bipolar and unipolar families collected in Toronto and in Rochester, N.Y., by Stancer and Weitkamp et al.; and five published Old Order Amish pedigrees collected by Egeland et al. showing strong evidence of linkage to chromosome 11 for bipolar affective disorder.

A focus of the analytic approaches in this volume is the accommodation of genetic heterogeneity. Such heterogeneity can occur in numerous ways. Elston and George discuss inclusion of covariates that may affect familial risk analysis of family data, based on logistic regression-type models appropriate for family data. One section is devoted to Bonney's regressive models, incorporated in user-friendly genetic analysis software being developed under Elston's direction.

Another section of the book concerns segregation analysis and related matters, in which the goal is to build a mathematical model that fits the transmission of (usually) a single trait in nuclear families or pedigrees. The modeling may be based on the Mendelian segregation of a single gene, the assortment of polygenic factors in the family, or random or systematic environmental factors such as sibship environment (the chapters by Demenais and Abel and by Hopper).

Extrafamilial sources of influence such as cohort and period effects can also be incorporated, as shown by Gilligan and Rice in an analysis of the NIMH Family Study data.

The papers concerning linkage relationships between affective disorder and specific genetic markers are, perhaps, the centerpiece of the book. Martinez et al. discuss the effects on linkage analysis of misclassification of affective disorder in relatives, and Greenberg and Hodge take up the effects on linkage analysis of the intrusion of a second gene that affects the penetrance of a first gene (epistasis). A three-allele model to account for the fact that bipolar and unipolar affective disorders occur in the same family is proposed, fit, and tested by Sandkuyl and Ott. Van Eerdewegh offers modifications of existing linkage programs to take account of cohort effects and of large, highly inbred pedigree structures. (Older linkage programs could deal with inbreeding either not at all or only in small quantities. In groups such as the Old Order Amish there is a lot of inbreeding, and this can strongly affect the results of linkage analysis under certain circumstances.) A relatively efficient, inexpensive method of screening for linkage is the affected sib-pair method, and Chakarborty discusses using this method to detect linkage of sex-linked dominant diseases. Wilson argues against the conventional habit of using peak lod scores as the sole summary statistic for deciding whether there is evidence for linkage. She suggests a Bayesian approach that takes into account the whole lod curve. Finally, the controversial issue of HLA and affective disorders is taken up in three papers that do not achieve a convergence of results. Weitkamp and Stancer's analysis suggests that there is an HLA-linked gene for susceptibility to affective disorder, whereas Price finds the opposite. I find the case more convincing on the negative side.

This is a complex book, parts of which are mathematically rather sophisticated. The editing shows few lapses. There is a missing leading term in the second equation on page 58, and there are several small errors in the chapter by Hopper (e.g., equation 31 on page 237). Although these do not detract from the readability of the manuscript for those familiar with mathematical models, it is a pity they crept into a book that might be read by nonspecialists.

Genetic analyses, in particular linkage analyses, are going to become more important in psychiatric research over the next few years. This volume is a good, up-to-date account of some of the more recent methodological advances that have been made in human genetic modeling. The importance of the progress being made is that complex phenotypes like psychiatric disorders require complex models. Environmental effects, cohort effects, effects of age at onset, familial heterogeneity in disease manifestations, and very likely genetic heterogeneity between the sources of genetic variability from one family to another all plague the analysis of psychiatric family data. Hitherto, analysts have mostly had to ignore the complications, because the available analytic methods were not up to dealing with them. We can look forward to a future in which data will not have to be forced into models in a Procrustean fashion but, instead, more or less satisfactorily incorporated. I recommend this volume to readers who need an introduction to the current state of knowledge in genetic statistics related to psychiatric family data.

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NEUROPEPTIDES

Neuropeptides in Psychiatric and Neurologic Disorders, edited by Charles B. Nemeroff. Baltimore, Johns Hopkins University Press, 1987, 310 pp., $45.00.

The time between a neuropeptide's discovery and its implication in disease states is usually brief, which, along with the exponential rate at which new neuropeptides are being defined, guarantees that clinical research findings involving this class of neurotransmitters will continue to proliferate. However, since the early stages of any novel research enterprise are often dogged by methodological issues and questions of reproducibility, many early "neuropeptide" findings will almost certainly be amended or refuted. To present a critical yet coherent perspective of such a changing body of data is a formidable enterprise for any editor. Dr. Nemeroff has acquitted himself admirably. He and his distinguished contributors have produced an edited collection that is neither repetitive nor discontinuous and is eminently understandable to anyone with an interest in clinical neuroscience.

One might be advised to approach *Neuropeptides in Psychiatric and Neurologic Disorders* by reading the last chapter first. In it Dr. Widerlov offers a welcome overview of the establishment of neuropeptides as bona fide neurotransmitters and provides an outline of the other chapters. The collection delivers what it promises. Apart from a review of the peptidergic neuron, the subject matter is oriented to human disease states. A general discussion of neuropeptides as diagnostic research tools is followed by a series of chapters each devoted to a specific pathophysiological condition. These include schizophrenia, manic-depressive illness, dementia, Huntington's disease, Parkinson's disease, sleep disorders, and pain. This classification permits authors to cross usual boundaries and present data from a multiplicity of research approaches, ranging from post-mortem neurochemistry to neuropeptide challenge paradigms. Given the youth of this research area, the reader should not be surprised that authors have drawn generously from basic sciences and may devote a good deal of effort to discussions of confounding factors while presenting often disparate results from their own and their colleagues' work. Although those new to neuropsychiatric research may wish for less hypothesizing and more dogma, the authors must be commended for avoiding overgenerous interpretation.

Since neuropeptides are not used as routine clinical diagnostic or treatment tools at present, this edited collection will find its greatest favor with two groups—those researchers interested in clinical implications of neuropeptides in general and those investigators in psychiatry and neurology who want to know how neuropeptides might be involved in a specific clinical state. Dr. Nemeroff and his collaborators have provided the best and most comprehensive reference on neuropeptides in neuropsychiatry available to date. The rapid developments in their field demand a sequel.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Ritualistic Use of Fluoxetine by a Former Substance Abuser

SIR: Much has been written regarding the benefits as well as the unwanted effects of fluoxetine (1–4). To the best of our knowledge, there have been no reports of an antidepressant effect associated with its ritualistic use by a former substance abuser.

Ms. A, a 33-year-old woman with dysthymia, avoidant personality, and polysubstance abuse, entered psychotherapy to address lifelong issues of depression, shyness, and fear of rejection, particularly in relation to men. Her drug and alcohol use was a "soothing" experience that allowed her to withdraw from a rejecting and critical world. Fearing that her addiction was preventing the attainment of her goals, she had made the decision to stop using drugs.

Despite a period of psychotherapy without drug use, Ms. A made minimal progress. After her concerns regarding addiction had been addressed, a trial of fluoxetine, 20 mg every other day, was initiated, but the dose was soon decreased to 10 mg every other day because she reported overstimulation. This dose of less than 20 mg required that she open the capsule. Within 2 weeks she had titrated the dose to between 1 mg every other day and 1 mg every day, depending on her desired energy level. This was done by emptying 1 mg of white fluoxetine powder onto a plate. With her illicit drug experience, "the dosing was simple." She ingested the powder by sucking it into her mouth and described the experience as similar to "speeding"—giving her increased energy and the ability to interact socially with others. She stated that using more than 1 mg/day caused excessive stimulation and that ingestion of less than 1 mg every other day caused severe drowsiness. Now, 7 months later, at a dose of 1 mg every other day, her appearance has improved, she has made social contacts, and she is making good use of psychotherapy. She often reports feelings of euphoria but shows no signs of mania or excessive stimulation.

Although 20 mg/day is the standard antidepressant dose, clinical experience with fluoxetine indicates that a lower dose is often sufficient, and patients open the capsule for this purpose. However, a dose of 1 mg every day or every other day is unusual. It is possible that this low dose has a positive physiological effect in a person with lifelong dysthymia. Indeed, patients often respond to minimal doses of neuroleptics and antidepressants. It is also possible that the low dose has a placebo effect derived from Ms. A's reenactment of her illicit drug use. Like addicts who become excited when visiting a place where they have previously used a drug, this patient got both excitement and comfort from recapitulating an act that had provided relief and safety in the past. It is also possible that her account of "speeding" might describe euthymia in a person who has been depressed much of her life.

Because of fluoxetine's popularity, other interesting reports are likely to appear. For example, anecdotal reports from Italy indicate that a new "illicit" drug known as "byebye blues" has been identified as fluoxetine.

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A Case of Amitriptyline Abuse

SIR: I wish to report on a case of amitriptyline abuse for euphorogenic effect.

Ms. A, a 24-year-old abuser of alcohol and cannabis, consulted her family physician because of anxiety, depression, and insomnia. Unaware of her drug abuse, he prescribed amitriptyline, 200 mg. About 30 minutes after taking each dose, she would experience relief from her symptoms that lasted about 2 hours. By increasing the dose, she found she could intensify these effects and prolong them for up to several hours. Her "high" consisted of feelings of relaxation, giddiness, and contentment. Frequently, this progressed to incoordination, slurred speech, and confusion. Sometimes she would forget how much she had taken and ingest up to 2 g. This intoxication was often followed by sleep and retrograde amnesia. These effects developed quite apart from concurrent use of other drugs and, in fact, amitriptyline became her recreational drug of choice.

Six months after beginning amitriptyline, Ms. A was brought to the hospital in an unresponsive state. An ECG showed sinus tachycardia of 100 bpm and a widened QRS interval. A neurologic examination showed coma, dysconjugate gaze, hyporeflexia, and pupils 4 mm and reactive. Her serum amitriptyline level was 1131 ng/ml. Two days later her sensorium was clear. She emphatically denied that she had attempted suicide and showed no signs of depression.

Ms. A continued her amitriptyline abuse. She was arrested for erratic driving; when results of a breathalizer test were negative and the blunting of her senses worsened,

police brought her to the hospital, where she was readmitted, this time with an amitriptyline level of 1573 ng/ml. After her condition was stabilized, Ms. A was transferred to the psychiatric unit. Examination showed moderate dysphoria but absence of neurovegetative changes, psychosis, cognitive impairment, or suicidal ideation. Consistent with antidepressant withdrawal effects, she experienced nausea and vivid dreams, which cleared after several days.

When confronted, Ms. A acknowledged her misuse of amitriptyline. She confessed that she was frightened because her craving had twice almost led to a lethal overdose and that she thought she was addicted to the drug. She began attending Alcoholics Anonymous and, upon discharge from the hospital, sought counseling for substance abuse.

The physiologic basis for amitriptyline's euphorogenic effects in this patient is not clear. I hypothesize that central anticholinergic effects were responsible. The patient's reports of tiredness, confusion, and ataxia are consistent with anticholinergic intoxication, and the withdrawal symptoms were quite characteristic of "cholinergic overdrive" (1). Abuse of other agents with this anticholinergic potential is common (2). Among antidepressants, amitriptyline has the most potent antimuscarinic effects. It is also possible that amitriptyline's effects on norepinephrine and serotonin metabolism were contributory.

Most clinicians do not worry about abuse when prescribing tricyclics. Standard psychopharmacologic texts do not warn of it. This case suggests that with known abusers of chemicals, it might be prudent to prescribe tricyclics with low anticholinergic potency or avoid their use altogether.

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Perphenazine in Breast Milk and Serum

SIR: Breast-feeding is generally not recommended if the mother is being treated with neuroleptic drugs. If a lessening of this restriction is to be considered, the magnitude of the 24-hour dose that would be passed on to the child must be ascertained. We have just had the opportunity to measure the concentration of perphenazine in breast milk and serum at steady state at two different dose levels. Collection of milk at both dose levels made it possible to calculate the 24-hour transfer of the drug to the milk. Furthermore, fractional collection of the milk enabled us to measure whether the concentration of perphenazine in breast milk follows the peak concentration in serum.

Ms. A, a 22-year-old mother, was admitted to a psychiatric hospital because of a postpartum psychosis. Her child was 1 month old and weighed 3.5 kg. The mother was given oral perphenazine, 24 mg/day, divided into two equal doses administered at 8:00 a.m. and 8:00 p.m., and milk was collected during 24 hours. Because of extrapy-

ramidal side effects and the high serum concentrations that were found, the drug dose was reduced to 16 mg/day, but it was still administered in equal doses at 8:00 a.m. and 8:00 p.m. This time milk was collected during three 4-hour periods from 8:00 a.m. to 8:00 p.m. and one 12-hour period from 8:00 p.m. until the next morning at 8:00 o'clock. The concentration of perphenazine in serum and breast milk was determined by high-performance liquid chromatography (1).

At a 24-hour intake of 24 mg of perphenazine, or 480 µg/kg, the drug concentration in the milk was 7.8 nmol/liter (3.2 ng/ml). The 24-hour milk production was 510 ml; thus, 1.59 µg of perphenazine per 24 hours, or 0.45 µg/kg, would have been passed on to the child. This amount of milk must be considered normal when artificial stimulation is involved. The reduction of the perphenazine dose to 16 mg/day (240 µg/kg) led to a proportional decrease in the mean concentration in the milk to 5.3 nmol/liter (2.1 ng/ml), corresponding to a daily transfer of 1.06 µg, or 0.3 µg/kg, of perphenazine to the child.

The serum perphenazine concentrations in blood samples drawn in the morning 12 hours after the last dose at both dose levels were 12.0 and 4.9 nmol/liter (4.9 and 2.0 ng/ml), respectively, corresponding to mean ratios of milk to serum of 0.7 and 1.1.

The perphenazine concentrations in the milk produced during the three 4-hour periods were 4.4, 7.6, and 5.0 nmol/liter (1.8, 3.1, and 2.0 ng/ml), respectively. The concentrations in serum from blood samples drawn in the middle of the three periods were 5.0, 8.3, and 7.0 nmol/liter (2.0, 3.4, and 2.8 ng/ml), respectively. Thus, the perphenazine concentrations in milk and serum roughly followed each other. The concentration in the milk produced during the night was 5.1 nmol/liter (2.1 ng/ml).

These results indicate that the ratio between the concentrations of perphenazine in breast milk and serum is of the same order of magnitude as those found for other neuroleptic drugs, i.e., about 1. Expressed as micrograms per kilogram of body weight, the dose passed on to the child with the milk was about 0.1% of that given to the mother. On the basis of this finding, breast-feeding was started. The perphenazine treatment lasted for 3½ months; during this period, the child thrived normally, and no signs of drug-induced symptoms developed.

The method we used differs from that of most other studies in that the measurements were done on the total 24-hour milk production and not on samples taken before and after feeding, which may give different results because of differences in the lipid content of the milk (2–4).

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A Residency Training Clinic in a County Jail

SIR: The psychiatric needs of inmate populations are often neglected (1). This may be due in part to professionals' resistance to working with these patients. Positive training experiences with such patients might help alleviate the discomfort of professionals and the manpower shortage as well.

A computerized literature search of MEDLINE back to 1966 and of *Psychological Abstracts* back to 1983 found only one description of a medical student training experience that involved inmates (2) and no such reports for graduate medical education. It is possible that such training goes unreported. Nevertheless, we want to report on a successful residency training program that was held in a county jail.

The Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina and the Charleston Area Community Mental Health Center (CMHC) organized a weekly 2-hour psychiatric clinic at the Charleston county jail (300 inmates) with the goal of addressing the needs of this underserved group and desensitizing psychiatric residents to this population. A faculty psychiatrist, a resident, and the jail's chief nurse provided psychiatric assessment and treatment. Emergencies arising outside the clinic's scheduled time were managed through a preexisting system that involved the transportation of inmates to our facilities at the CMHC or to the emergency room.

Before the establishment of the clinic, all inmates were transported from the jail to our health facilities for services. This transportation presented an incentive for inmates to feign illness as a way of getting time out of jail, often confounding the validity of the residents' evaluations. This frustrating experience resulted in an even greater aversive response to the patients.

The residents' evaluation of the project was very favorable. They valued learning about the local criminal justice system. They received on-site, in vivo clinical supervision and were able to observe the attending psychiatrist interview patients. With the removal of the motivation for feigning illness, validity of their clinical assessments was improved.

The availability and use of preexisting information in the CMHC files led to early identification of high-risk individuals and to effective interventions in an effort to prevent decompensation while they were incarcerated. Inmates who might not have been served because of difficulties in transporting them were receiving services efficiently on site, possibly averting decompensation and more dangerous crisis situations.

The system significantly reduced the county sheriff's manpower and vehicle use for transporting inmates. The sheriff, impressed with the effectiveness of the clinic, shared his enthusiasm with several other sheriffs in the state. This resulted in the South Carolina Department of Mental Health's sponsoring of a conference for sheriffs and jail administrators on working with the mentally ill in jails, which featured the Charleston clinic as a model program.

The project represents an example of a successful public-academic collaboration. It produced obvious benefits to all parties involved and was highly regarded by the community.

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Desipramine and Its 2-Hydroxy Metabolite in Patients Taking or Not Taking Methadone

SIR: The article by Iradj Maany, M.D., and associates on increase in desipramine serum levels associated with methadone treatment (1) was a well-done and interesting examination of the observation that methadone patients treated with desipramine for cocaine abuse require lower doses of desipramine to attain therapeutic blood levels of the parent compound (2). Our further examination of this phenomenon has taken a different direction, however, by comparing the metabolic disposition of desipramine in patients taking methadone to that of patients not taking methadone.

We have examined the 2-hydroxy metabolite of desipramine and compared it in 11 methadone patients and 61 patients not maintained on methadone—39 with depression and 22 with cocaine abuse (3). All patients were stabilized at a fixed dose of 2.5 mg/kg of desipramine before blood level assessment. The patients' lowest plasma concentrations of desipramine and its unconjugated 2-hydroxy metabolite were determined by means of a modified high-performance liquid chromatography technique (4).

The 11 cocaine abusers who were concurrently maintained on methadone had a significantly lower ratio of desipramine dose to plasma concentration (mean±SD=0.9±0.4) than the depressed patients (2.2±1.9) and the nonmethadone cocaine abusers (2.0±1.6) (F=4.8, df=2, 70, p<0.05). The 2-hydroxy metabolite-desipramine ratios also were significantly lower in the methadone patients (0.19±0.16) than in the other 22 cocaine abusers (0.39±0.26) and the depressed patients (0.50±0.31) (F=7.7, df=2, 70, p<0.01). This difference was not due to desipramine dosage or abuse of cocaine.

Methadone is extensively metabolized by the hepatic microsomal enzymes, with production of N-demethylated cyclic metabolites of methadone, which are then hydroxylated and excreted in bile and urine as water-soluble glucuronide conjugates (5, 6). Hydroxylation is also a key metabolic step in desipramine metabolism (4). However, as an explanation for our data, inhibition of hydroxylation of desipramine by methadone must be considered conjectural. More definitive pharmacokinetic studies on this mechanism, including studies of urinary desipramine and its metabolites and an assessment of conjugation, will require a design similar to Dr. Maany and associates' inpatient study, where patients can be administered desipramine when taking and not taking methadone. Together, these two sets of data support such a mechanism and suggest the need for lower desipramine doses and plasma desipramine monitoring in methadone-maintained patients.

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Suicidal Preoccupation During Fluoxetine Treatment

SIR: A report by Martin H. Teicher, M.D., Ph.D., and associates (1) described six depressed patients who, upon relatively brief exposure to fluoxetine, developed "intense, violent suicidal preoccupation." The suicidal thoughts were "obsessive, as they were recurrent, persistent, and intrusive." The investigators were somewhat puzzled by this finding given that fluoxetine, a potent serotonin reuptake inhibitor, is used to control obsessive-compulsive symptoms. While the authors gave an impressive list of likely and unlikely explanations, we believe that the specific pharmacologic effects of fluoxetine should be emphasized as a probable etiologic factor. We propose that the phenomenon they observed may be the equivalent of the serotonin reaction described in patients with obsessive-compulsive and panic disorders rather than simply "a paradoxical response in some patients."

We have used fluoxetine extensively in the treatment of patients with obsessive-compulsive disorder (2). Some of these patients' initial response to fluoxetine was a transient worsening of their obsessions and compulsions. Our original dosing schedule called for a 20-mg increase every 2 days. We quickly learned that a much slower increase (20 mg every 2 weeks) practically eliminated this reaction. We hypothesized that a sudden increase in serotonergic transmission is responsible for this "paradox." Furthermore, we speculated that only chronic treatment with fluoxetine will result in postsynaptic serotonergic desensitization and subsequent antiobsessional effect. A similar reaction has been described as the serotonin reaction in fluoxetine-treated patients with panic disorder (3). Since even 20 mg of fluoxetine, the only available dose at present, seems too high, the recommended starting dose for panic patients has been reduced to 5 mg/day (4).

Dr. Teicher and associates did not specify whether their depressed patients had histories of obsessions, compulsions, or panic attacks. However, many depressed patients, even without histories of obsessive-compulsive disorder, exhibit obsessional ruminations and brooding during a depressive episode. The content of these ruminations is frequently related to suicide. Five of the six patients the authors described had histories of suicidal thoughts, and four of the five had made suicide attempts or gestures. The patients were exposed to fairly high doses of fluoxetine within a relatively short time period. It is conceivable that this serotonergic challenge with fluoxetine accentuated the obsessional ruminations to the extent of severe suicidal preoccupation. Depression may be associated with a symptomatically similar but more prolonged serotonin reaction than that exhibited by patients with obsessive-compulsive or panic disorders.

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Dr. Teicher and Associates Reply

SIR: Drs. Papp and Gorman have formulated an interesting and important hypothesis. In our report three of the patients (cases 4, 5, and 6) had histories of rare or infrequent panic attacks but fell short of fulfilling the DSM-III-R criteria for panic disorder. One patient (case 2) had a history of obsessional thoughts in childhood that had abated, but in the midst of his depression he did display some checking behavior. The patient in case 4 also had a history of obsessive ruminations during depression. Thus, many of our reported cases may have been at increased risk according to the hypothesis of Drs. Papp and Gorman.

We have also received information regarding a number of possible additional cases, which further strengthens this hypothesis. One woman with obsessive-compulsive disorder wrote that she developed obsessive suicidal ruminations following her first 20-mg dose of fluoxetine, but she indicated that these suicidal thoughts abated over the course of treatment in conjunction with her preexisting obsessions. We also received reports from two psychiatrists describing the emergence of suicidal ideation that began 2 weeks after initiation of fluoxetine (20 mg) to treat obsessive features in three adolescents with Tourette's disorder. Finally, we received one report from a physician of a suicide by hanging that occurred 2 weeks after initiation of fluoxetine (20 mg) in a 15-year-old adolescent with obsessive-compulsive disorder who had little or no preexisting depression. Thus, obsessive-compulsive symptoms may be a relative risk factor, and patients with these symptoms may benefit from initiation of treatment with lower doses and more gradual titration.

While it is tempting to postulate that these suicidal obsessions may be part of a specific serotonin reaction resulting from a sudden increase in serotonin neurotransmission, we should be cautious about accepting this hypothesis until more direct neuropharmacologic data are available. The time

course of emergence of suicidal ruminations in the majority of these cases is not entirely consistent with a sudden increase in serotonin neurotransmission. Other possible neuropharmacologic effects can include drug-induced alterations in the circadian regulation of serotonin release (1), differential changes in the relative regional receptor densities or second-messenger coupling of some of the multiple serotonin receptor subtypes (2), or alterations in the balance between serotonergic neurotransmission and other coupled neurotransmitter systems (3). Nevertheless, Drs. Papp and Gorman have presented a very interesting hypothesis that enhances our thinking about this complex phenomenon.

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Psychiatric Illness in Relatives of Patients With Bulimia Nervosa

SIR: We read with interest the article by Joy A. Kassett, M.S.W., M.P.H., and associates (1) reporting higher rates of major affective disorders, eating disorders, and alcoholism in first-degree relatives of 40 patients with bulimia nervosa who had never suffered from anorexia nervosa than in first-degree relatives of 24 normal control subjects. We would like to comment on several aspects of their report.

The interviewers of relatives in this study inquired about the presence of psychiatric illness in the control probands and thus were not blind to whether the relatives belonged to families of bulimic or control subjects. Such knowledge could have influenced the way the relatives were interviewed or given diagnoses. Although one of the authors has reported on a very well-designed study (2) in which knowledge of patients' prior psychiatric diagnoses did not affect their diagnoses at subsequent interviews, we are not aware of any studies in which the diagnoses of relatives were shown to be unaffected by knowledge of probands' diagnostic status.

The control probands in this study consisted of individuals with no history of any psychiatric disorder. Assuming a genetic basis for at least some psychiatric disorders, one would expect to find lower rates of psychiatric illness in the relatives of such control subjects than in members of the general population studied in the same manner. Thus, it seems difficult to argue from the results of this study that the rates of affective or other psychiatric disorders are higher in the relatives of normal-weight bulimic probands than in the general population.

The authors did not report how many of their bulimic probands were inpatients—a potentially important point, since individuals with normal-weight bulimia are usually treated as outpatients. If a relatively high proportion of these probands were inpatients, it raises the possibility that the

bulimic subjects in this study were more seriously ill than most patients with this diagnosis. Together with our other concerns, this is another reason to be cautious about generalizing from these results to the population of all persons with normal-weight bulimia.

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Ms. Kassett Replies

SIR: My associates and I would like to make several comments on the three points Dr. Stern and colleagues make concerning the validity of our family study.

The question of validity is raised in reference to whether the diagnostic interview—the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L)—was administered by persons blind to the relatives' membership in bulimic or control families. It was. The interviewers were blind to proband (bulimic and control) diagnosis in two-thirds of the interviews of relatives. In the interest of having a properly blind study, the interviewing of relatives was distributed among persons who were simultaneously conducting other family studies of schizophrenia, schizoaffective illness, and manic-depressive illness. The interviewers used a systematic family history interview to obtain diagnostic information from each interviewee about all first-degree relatives of the proband. The SADS-L was completed before the family history part of the interview was done, so that it was, in fact, given blindly. Two clinicians then blindly diagnosed the relatives from the information obtained with the SADS-L, and any disagreements were resolved in a study staff meeting, where the blind nature of the study was maintained.

The question of representativeness of sampling is raised with respect to both the control probands and the bulimic probands. The purpose of the study was to compare rates of illness in normal healthy control subjects, not rates of illness in the general population. This is a proper comparison for detection of the familial psychopathology that is particularly useful in studying common diseases (1). An advertisement for normal volunteers for a National Institute of Mental Health study was placed in a local newspaper and in the National Institutes of Health normal volunteer office. No mention of families was made. Of 45 volunteers, 30 were accepted as normal probands.

Proband selection is not a legitimate issue on which this

study can be faulted. Some bulimic patients were hospitalized, and this was stated. However, they were selected because they met diagnostic criteria. There are no a priori reasons to hypothesize that they were different from bulimic outpatients. In the case of affective disorder, it has been shown that the same rates of illness are observed in relatives of hospitalized and nonhospitalized unipolar patients who meet the same diagnostic criteria (2).

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JOY A. KASSETT, M.S.W., M.P.H.
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Right Versus Left Unilateral ECT

SIR: We wish to make the following observations on the report of Richard Abrams, M.D., and associates (1) that left unilateral ECT is more efficient than right unilateral ECT. First, the electrical charge delivered was much greater than is conventional for unilateral brief-pulse ECT. Second, the margin of difference between the two forms of ECT (about 4 Hamilton units after six ECTs), while statistically significant, may not be clinically significant. Third, there was no comparison (between the two ECT groups) of the patients who were clinically considered to have responded; the data suggest that no difference is likely.

Although, to their credit, the authors refrained from recommending the use of left unilateral ECT in preference to right unilateral ECT, we raise these issues lest the casual reader interpret the report to suggest that there is a therapeutic advantage in using a form of ECT known to carry a considerable risk for cognitive deficits.

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Dr. Abrams and Associates Reply

SIR: Drs. Andrade and Gangadhar are battling a straw man, since we did not report greater efficiency of left than right unilateral ECT; indeed, both the discussion and abstract sections of our article clearly stated that we found the two methods to be "not significantly different in overall antidepressant potency." Moreover, their claim that left uni-

lateral ECT carries "a considerable risk for cognitive deficits" is not supported in the literature.

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Late-Onset and Early-Onset Schizophrenia

SIR: Dr. Felix Post, who has written much about this topic, once said to me, "To be quoted is very nice; to be quoted correctly is too much to expect." I was reminded of this when reading the article by Godfrey D. Pearlson, M.D., and his colleagues (1). They suggested that my associate and I (2) found CT changes in similar proportions of early- and late-onset schizophrenic patients. Our article, however, made no such comparison. In fact, whereas only a proportion of young schizophrenic patients show enlarged cerebral ventricles, our patients with "late paraphrenia" showed a uniform enlargement that was normally distributed. We have, furthermore, made it clear that this was purely a ventricular phenomenon and that there was an uncoupling of the usual association between ventricle enlargement and sulcal widening which occurred in an age-matched control group (3). The long-term follow-up that the authors recommended has in fact already been reported (4). It demonstrated that although the previously reported (2) mild cognitive impairment increased slightly after a mean follow-up of 3.7 years, memory and orientation scores remained above the cutoff point for diagnosing dementia. These subjects therefore did not develop Alzheimer's disease, although an even longer follow-up may show different results.

In their understandable wish to pursuade Americans that schizophrenia with an onset after 45 years of age does exist, the authors have either misread or misquoted the "European" literature. They have prematurely assumed an identity between late paraphrenia and schizophrenia and have ignored differences in definition of the term "late onset." Both M. Roth and F. Post used the age of 60 as a dividing line. Post, in particular, stressed the heterogeneity of his cases, which he cautiously referred to as "persistent persecutory states." Holden reported on patients over the age of 65, and the heated correspondence in the columns of the *British Journal of Psychiatry* that followed his paper showed some disagreement about the proportion of patients who demonstrated Schneiderian first-rank symptoms. We found these in only 16 of our 43 cases, whereas Grahame, using a different method of ascertainment, reported them in 14 of his 25 cases. There are no doubt some differences in the sampling frames used in different series, which are therefore not strictly comparable. In addition, in patients with an onset after age 60, the proportion with positive family histories is *not* as high as that for younger patients (5). Although not conclusive, the evidence from the human lymphocyte antigen status of young and old patients (6) suggests that these may be biologically different.

As we appear to be on the verge of a period of reexamination by modern neurobiological methods of the whole problem of delusions and hallucinations in the elderly, it is probably wise not to adopt an unduly rigid approach to the question of whether these represent cases of late-onset schizophrenia. Most evidence suggests that this may be an oversimplification. Having said that, provided our diagnostic systems allow us to retrieve these cases easily, it does not

matter what we call them. Retrieval can be achieved either by calling the patients schizophrenic and coding for age at onset or by using terms such as "late paraphrenia" or "late-onset delusional states."

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PROF. RAYMOND LEVY
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Dr. Pearlson and Dr. Rabins Reply

SIR: We feel most undeserving of Professor Levy's wrath. First, our article did not quote him at all. We observed only that both his CT data on late-life-onset schizophrenia ("late paraphrenia") (1) and our own (2) showed nonspecific brain changes similar to those reported by ourselves and others (3, 4) in CT studies of patients with more typical early-onset schizophrenia.

Second, we carefully reviewed the European literature on schizophrenia with late-life onset, retranslating the most important original German contributions into English with the aid of two German-speaking psychiatrists. The fact that we may have reached different conclusions from those of Professor Levy hardly implies that we must have "misread or misquoted" these sources. Our article spoke to two audiences: the American, to challenge the idea that schizophrenia cannot occur after age 45, and the British, to reexamine ideas on late-onset cases, however defined. Accepting age 60 (or 65) as a cutoff is one such assumption. (The mean age of our late-onset group was, in fact, 61 years.) Our map reassures us that Britain and Germany remain "European."

We are not wedded to the idea that late paraphrenia is identical to classic schizophrenia; the absence of both prominent thought disorder and affective flattening in late-onset cases are two significant differences that were emphasized in our article. One should bear in mind that schizophrenia with onset early in life may also not be a unitary entity, but that useful testable hypotheses can be generated from this assumption.

We too have observed the "heated correspondence" in the British psychiatric literature generated by the topic of late-life hallucinatory/delusional states. It should be noted that light, rather than heat, is the desired product. Instead of importing this sometimes acrimonious debate from across the Atlantic, we heartily support Professor Levy's suggestion to remain open-minded.

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Violent Behavior Among Schizophrenic Patients

SIR: The study by Menahem I. Krakowski, M.D., Ph.D., and associates on the prediction of violent behavior (1) addressed a timely subject. However, we see various problems with the article as presented. The authors started off with the inflammatory statement that "violence is frequently reported in schizophrenic inpatients." This is the type of unsupported pronouncement that the field of psychiatry is trying to avoid, and in fact it was the subject of last year's American Psychiatric Association theme, "Overcoming Stigma." The references the authors cited do not support their view. The study by Tardiff and Sweillam (2) indicated that among the subjects studied, the proportions who had had violent episodes during the preceding 3 months amounted to 6.6% among schizophrenic inpatients and up to 14.1% for other diagnostic groups. Data from another reference in the article (3) also contradicted the authors' statement: the rate of violent episodes (including assault plus suicide attempts) was 7.9% for schizophrenic patients, 10.3% for those with organic brain syndromes, and 23.3% for "others." In fact, it is not at all clear that the rate of violence for schizophrenic inpatients is any higher than that for healthy individuals in group living situations such as nursing homes and boarding schools. We have further noted methodological problems with the study.

Ratings were done blindly for "low violence" versus "high violence" subjects only, while the distinction between control and violent subjects was open. Thus, only comparisons between the first two groups are meaningful. But how were these two groups operationally defined? Verbal abuse was assumed to fall on a continuum of violence that also includes battery. A person repeatedly threatening another would be rated a high violence subject, whereas a person who beats up another person only once would be given a rating of low violence. We are surprised that the authors did not use any of the available well-validated scales that measure degree of violence, such as the Overt Aggression Scale (4), and long-term violent tendencies, such as the Buss-Durkee scale (5). Besides, many potentially important variables were based on self-reports, specifically, arrests and convictions for violent crimes and head trauma. The authors discussed the possibility of neurological impairment as secondary to violence solely on the basis of these self-reports, when more objective data should have been obtained.

Another problem is the use of chlorpromazine equivalents to control for medication. High- and low-potency agents are

clearly associated with different side effect profiles, especially neurologically. It could certainly be argued that impairments in hopping, tandem walking, and walking-associated movements might more accurately reflect medication effects than variables associated with violent schizophrenic patients. The scale that was used to quantify neurological signs was designed by the authors but not described in any detail. As it has not been published in a peer-reviewed periodical, access and critical evaluation by readers of the article would be difficult. Assuming that the scale is valid, the authors are still left with the finding that only four of the 56 items tested distinguished between high- and low-violence groups at significance levels of $p < 0.05$, and one at $p < 0.01$. Obviously, if we look at a large-enough number of variables in two groups, we will find some that distinguish between the two. There is no compelling face validity underlying the suggestion that graphesthesia, for instance, is more pronounced in violent persons with schizophrenia.

Finally, in their discussion, the authors introduced a *deus ex machina*: violent behavior and neurological abnormalities may really relate to a third variable, not previously considered, namely, type of schizophrenia. These speculations are not supported by any primary database in the body of the article.

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Dr. Krakowski and Associates Reply

SIR: Is violence frequently reported in the literature? The fact that 11 of 13 studies on violent psychiatric patients mentioned schizophrenia as one of the "over-represented diagnoses" (1) justifies that statement. We included two studies by Tardiff and Sweillam because they reported that assault outside of hospitals was related to a greater likelihood of paranoid schizophrenia and assault in hospitals to nonparanoid schizophrenia.

The nonblind ratings of violent versus nonviolent patients were far from meaningless. The clinicians who administered the neurological examination were not told anything about the purpose of the data collection. Furthermore, the differences between the high and low violence groups that we obtained, under blind conditions, corroborate the validity of comparing nonviolent and violent subjects.

Dr. Graham and his colleagues miss the point of the distinction between low violence and high violence. The emphasis was not on the seriousness of incidents; the data we presented suggest that frequency of assaults is an important

dimension and that the various assaultive behaviors, although vastly different in impact on the victims, have the same neurobiological underpinnings.

It is possible, however, to use our data to address concerns about type and severity of assaults. Physical assaults were positively correlated with verbal (Pearson's $r = 0.58$, $p < 0.001$) and property ($r = 0.47$, $p < 0.001$) assaults. If we divide violent patients into high violence, low violence, and nonviolent groups on the basis of physical assaults alone, they differ significantly in neurological impairment ($F = 6.2$, $df = 2, 83$, $p = 0.003$).

Dr. Graham and associates' concern that a person repeatedly threatening another would be rated high on violence is unfounded. None of the patients displayed trivial violence. Furthermore, after transfer to the secure care unit, only six of the 27 patients in the low violence group had further episodes of physical assault; none was severe.

The issue of the reliability of historical variables, especially criminal activity and head trauma, is raised. Our patients' self-reports of criminal activity were found to be reliable when they were compared to official arrest records (2). In addition, "historical information was obtained from hospital records and family members whenever possible" (p. 850).

The use of high-potency neuroleptics cannot account for the neurological differences. Our data indicate 1) no differences among the three groups in the number of patients who were taking high- versus low-potency neuroleptics ($p > 0.70$) and 2) no differences in neurological impairment between patients taking high- versus low-potency neuroleptics ($p > 0.80$).

The neurological scale is now available in a peer-reviewed periodical (3).

Differences in neurological abnormalities among the groups, as explained (pp. 850–851), were first analyzed globally; only when these were significant were further analyses attempted. Table 1 in the article presents legitimate post hoc exploratory analyses. As for the etiology of these abnormalities, there is evidence that more severe schizophrenia is associated with more severe abnormalities (p. 853), including defects in stereognosis, graphesthesia, coordination, etc. (4). The greater neurological impairment in the high violence group, and its nature, suggests an association between high violence and more severe schizophrenia.

We have some empirical evidence, as well, for this association from a subgroup of these patients who were administered the Brief Psychiatric Rating Scale (BPRS). High violence patients ($N = 12$) had a significantly higher BPRS score than low violence patients ($N = 13$) ($t = 2.27$, $df = 23$, $p < 0.05$). Moreover, neurological impairment was positively correlated with the BPRS total score ($r = 0.53$, $p < 0.01$) and the thought disorder factor ($r = 0.56$, $p < 0.01$).

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Psychotherapy for Depression

SIR: In his article "Toward a Clinical Model of Psychotherapy for Depression, I: Systematic Comparison of Three Psychotherapies" (1), T. Byram Karasu, M.D., discussed his concept of "the psychodynamic approach" clearly and comprehensively. I use a different definition and will give my reasons for so doing. The essential differences between our views hinge on our different understandings of the relations between psychoanalysis and a psychodynamic approach.

Dr. Karasu emphasized the approach's similarities to psychoanalysis, stating (in the tables) that a primary technique of the psychodynamic approach includes "fully or partially analyzing transference and resistance" and that the approach would include "personality alteration," would be of "indefinite duration" and be "open-ended," would include "transference regression" and the use of "free association," would "focus on past events and spontaneous associations," and would seek to "ensure maximal insight." Each of the preceding specialized techniques is appropriate in psychoanalysis; each of them invites uncontrolled disaster when used routinely or indiscriminately in psychotherapy. While psychoanalysis was a progenitor of dynamic psychotherapy, one should not equate an offspring with its parent.

Both psychoanalysis and dynamic psychotherapy are highly individualized forms of treatment, but the approaches are fundamentally different. In therapeutic psychoanalysis the content (the patient's gradual understanding of his or her unique psychodynamics) *follows* from the technique (a set of therapeutic principles developed to facilitate comprehensive self-understanding). The process is expensive in terms of time, money, and the dedication required of both participants. When successful, the benefits can far outweigh the costs. Repeated efforts to shorten the process have instead changed both the process and the results.

In dynamic psychotherapy the sequence is reversed. The content (the therapist's comprehension of basic psychodynamic principles introduced through reading and class discussions but most reliably learned from the supervision of his or her clinical work or from first-hand experiences as a psychotherapy patient) *precedes* the choice of the techniques judged most likely to be helpful to the particular patient.

Both forms of treatment proceed from a limited set of basic principles to a broad range of possibilities determined by how the principles apply to any individual patient. In psychoanalysis the sequence proceeds from the analyst's experience with the basic principles of psychoanalytic technique to the wide-ranging content of each patient's self-understanding. In dynamic psychotherapy the sequence proceeds from the therapist's understanding of the basic principles of psychodynamics to a wide range of individualized psychotherapeutic techniques.

In my experience, protracted stalemates in psychotherapy most frequently result from the therapist, the patient, or both having covert fantasies that they can achieve psychoanalytic results without the essential training, experience, and resources required for psychoanalytic success. Disappointing outcomes with dynamic psychotherapy are frequently seen with therapists who do not recognize (or, worse, do not respect) the differences between psychoanalysis and other forms of psychotherapy.

Inexperienced therapists frequently encourage (or fail to discourage) their patients from developing transference neuroses. These therapies then founder because the therapist and patient cannot possibly resolve the transferences that have been encouraged. The treatment stagnates as the patient's original problems are replaced by an unresolvable, structured transference.

Psychoanalysis is a relatively standard form of treatment. Psychotherapy, however, is a generic term covering a broad range of techniques. Psychotherapy covers a broad horizon, while psychoanalysis is limited to a narrow band of the horizon, which is studied in great depth.

I have tried to clarify what I regard as fundamental differences between psychoanalysis and a psychodynamic approach.

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GEORGE H. KLUMPNER, M.D.
Oak Park, Ill.

SIR: In regard to Dr. Karasu's article on the psychotherapy of depressive illness, I would like to suggest a simple protective mechanism for our patients. As part of major depressive illness, a patient's marriage, job, finances, and so forth look bad. Are these problems the obvious distortions caused by the illness, or are there real problems?

I refuse to deal with these problems until the patient has responded to medical treatment. In most cases the marriage, the job, the finances, and everything else seem satisfactory at that point. I have seen many patients seduced into long-term therapy for nonexistent problems that were assumed to be the causes of the illness.

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Dr. Karasu Replies

SIR: I very much appreciate the distinctions Dr. Klumpner has drawn between psychoanalysis and a psychodynamic approach. While I may have unwittingly stressed their similarities in order to contrast them with other modalities, I in no way meant to imply that they are synonymous. I too am aware of the perils of the inexperienced therapist in mistaking one for the other or, worse, in imposing on the patient expectations that do not conform to the type of treatment offered. In this regard, I refer readers to my recent chapter, "Psychoanalysis and Psychoanalytic Psychotherapy," in the *Comprehensive Textbook of Psychiatry* (1), in which I have much more directly carved out the similarities and the differences across the psychoanalytic spectrum.

In response to Dr. Huessy's letter regarding the use of medical treatment for depressed patients and the use of psychotherapy thereafter for problems that do not abate with medication, my article is in general agreement (and much of

the pharmacotherapy/psychotherapy research on depression now supports this). However, our reasons for this therapeutic orientation are decidedly different: Dr. Huessy sees the *withholding* of psychotherapy as protective of the patient, and I view the *utilization* of psychotherapy as protective, insofar as it can offer the most selective and comprehensive care.

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Diagnosis of Tourette's Disorder

SIR: I was particularly interested in the article on Tourette's disorder in a set of reared-apart triplets by Nancy L. Segal, Ph.D., and associates (1). As I am preparing to embark on a fellowship in child and adolescent psychiatry and am sure to be presented with patients with this disorder, I found the article well worth reading.

The authors studied a pair of monozygotic females and their male cotriplet with respect to symptoms they had which, according to the article, met the criteria for Tourette's disorder. The article clearly supports the hypothesis of genetic transmission of the disorder, since at least two of the three triplets had similar presentations, and the family pedigree indicated Tourette's disorder in the biologic father of the triplets and two of the children of one of the monozygotic females. I was struck, however, by the lack of a report of vocal tics in the male dizygotic cotriplet. Although he had multiple motor tics throughout his illness, no vocal tics were reported for him as were reported for the monozygotic females.

This appears significant in view of the *DSM-III-R* criteria for Tourette's disorder, which state that both multiple motor "and one or more vocal tics" must "have been present at some time during the illness." Thus, it seems that the dizygotic cotriplet in this study did not meet the *DSM-III-R* criteria for Tourette's disorder, as is implied in the article. In view of this apparent contradiction between clinical presentation and *DSM-III-R* criteria, a question is raised: Did the authors use some other diagnostic classification in determining the presence of Tourette's disorder? Clarification of this point would aid in determining whether we assign patients a diagnosis of chronic motor tic or Tourette's disorder (2).

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DARLENE C. IFILL-TAYLOR, M.D.
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Dr. Segal and Associates Reply

SIR: We thank Dr. Ifill-Taylor for pointing out the discrepancy between the diagnosis of Tourette's disorder in the male dizygotic cotriplet and the information provided in his clinical summary, in which an absence of phonic tics was indicated. We failed to note, however, that the second-born cotriplet did provide a history of vocalizations for her brother, as documented in the questionnaire on family members that she completed. A tendency toward denial of symptoms on the part of the brother was observed during the general physical examination; for this reason we relied on the sister's observations in the preparation of this report.

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MAURICE W. DYSKEN, M.D.
THOMAS J. BOUCHARD, JR., PH.D.
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Multiple Personality Disorder and Borderline Personality Disorder

SIR: A recent *Journal* article concerning multiple personality disorder (1) warned that this disorder with depersonalization, derealization, and identity problems must be differentiated from other *DSM-III-R* axis I disorders. Another article (2) indicated that "quasi-psychotic thought" (depersonalization, derealization, odd thinking) is more frequent in individuals suffering from borderline personality disorder. A third article (3) observed that "many of the reported long-term consequences of childhood sexual abuse are identical to *DSM-III-R* criteria for borderline personality disorder." Did this third article find a congruence between multiple personality disorder and borderline personality disorder? The severe traumas experienced by these borderline patients are the same as those described by patients with dissociative disorders, especially multiple personality disorder.

This conclusion contradicts the fact that multiple personality disorder is an axis I diagnosis while borderline personality disorder is found on axis II. However, clinically, multiple personality disorder is a lifelong constellation of coping strategies, more in keeping with an axis II diagnosis. Treating individuals with multiple personality disorder is little different from treating borderline personality disorder, considering the long, stormy course, the risk of suicide, and the difficult transference/countertransference problems. This may also clarify the confusions of multiple personality disorder coexisting with other axis I diagnoses. If we place multiple personality disorder on axis II by considering it a variant of borderline personality disorder, we can also include an acute axis I diagnosis.

In actual psychiatric practice, multiple personality disorder and borderline personality disorder have the same etiology, symptoms, and course.

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<div style="text-align:right">MARKHAM KIRSTEN, M.D.
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Psychotherapy Training for Psychiatrists

Sir: I am writing to register a global response to several articles in the *Journal*, specifically, Paul C. Mohl, M.D., and associates' vision of psychotherapy training for "the psychiatrist of the future" (1), the debate between Gerald L. Klerman, M.D., and Alan A. Stone, M.D., on standards of treatment (2, 3), and articles by Kenneth Z. Altshuler, M.D. (4) and Paulette M. Selmi, Ph.D., and colleagues (5).

The picture these articles create is of a future (and in some places, a present) in which a spiritless, mechanistic psychiatry has divested itself of the core discipline of psychotherapy. Patients will be diagnosed with standardized clinical interviews (perhaps by computer) and assigned to "therapists" who will administer standardized, "specific" short-term therapies from manuals. Some of those therapists will be computers—perhaps continuity of care will consist of the same computer for diagnosis and treatment! Having had no direct experience of the power of an empathic, individualized, and personal psychotherapy relationship to heal either their patients or themselves, residency graduates will be alienated from their own humanity and thus be at greater risk for inappropriate relationships with patients. Obsessed with specific and short-term therapies, trainers will lose sight of the *general*, endemic patterns of abuse and abandonment that underlie much psychiatric illness regardless of diagnostic category and that are typically not revealed or dealt with in a span of 10 or 20 therapy sessions.

Unlike the subjects of academic double-blind studies, our patients and medical colleagues will not be well served by this situation and will know it. They are already voting with their feet: patients are fleeing to psychologists and counselors, who, if not as well versed in physiology and neurology, at least remain centered on the unique personhood of their "clients," and other physicians are seeking out the same non-medical professionals to give them insight into their patients' problems, not just a *DSM* diagnosis and pharmacological advice.

Psychiatry, and medicine generally, will be impoverished if psychiatric training and practice ceases to have a human center in the process of psychotherapy.

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<div style="text-align:right">PAUL GENOVA, M.D.
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The Idiot Savant: A Reconsideration of the Syndrome

Sir: In his review of the idiot savant syndrome (1), Darold A. Treffert, M.D., considered the different studies on this disorder, looking for a possible justification of the surprising abilities of the patients afflicted with it. On the basis of the literature (2, 3), his starting point was to try to explain something that is inaccessible and extraordinary.

Our opinion is that a possible solution can result from a completely different way of approaching the problem. Are these subjects' capabilities truly astonishing? Certainly, we can assert that they are, if we refer to normality. However, we wonder whether, from a logical/formal viewpoint, it is really difficult to obtain such performances.

For this reason, we have tested the possibility of reproducing each of the savant's abilities with software programs. Our conclusion is that all these skills can be simulated either by plain data recording and reading operations or by short sequences of low-level instructions, executable by any elementary computing machine.

The point is that the savants' abilities aren't exceptional by themselves, but they appear so because our CNS lacks the proper means for doing these kinds of operations. The reason is that our philogenetic history never rewarded such a simple way of processing information but instead favored a more complex system in order to overcome the complicated problems with which human life had to cope during evolution.

A possible hypothesis is that these subjects have lost the ability to process complex information at a high level and to store data in an integrated way. The consequence of this lack of an integrated intelligence is that these individuals have the chance to understand some simple problems in their essence, free from the load of associations that a normal intelligence automatically creates. It is for this reason that they are able to elaborate and solve particular kinds of "simple problems" in a very fast way. Thus, this package of associations provides the essence of the human mind's power, fancy, and fertility but also explains why there are difficulties in solving simple and useless logical/formal problems.

We arrive at the same conclusion if we analyze the extraordinary memory capacities that some savants have. Their memories are completely rigid, capable of storing and recovering only single elements and a very small (or absent) number of associations. This type of memory is anomalous not in its dimensions but in its quality.

The purpose of this kind of approach to the savant issue is to show how all the apparently extraordinary skills of these subjects can be explained simply by placing them in the category of mental deficiency. This condition excludes most intellectual high-level control and associative faculties, thus increasing capabilities for some simple, but faster, processing.

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DR. MASSIMILIANO DIECI
A. MONTI GUARNIERI
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Dr. Treffert Replies

SIR: The hypothesis that some idiot savant abilities, particularly the characteristic rigid, unitary, and poorly associative memory they all display, could be the result of utilization of phylogenetically earlier, more primitive, and less associative memory pathways is one I did mention but could discuss only briefly in my review article. I have had the opportunity to explore this hypothesis in much greater detail in later work (1). There is reason to believe that the "memory without consciousness" (habit memory) seen in savants can be explained by their use of this more primitive circuitry as an alternative to a higher-level and more richly associative, but damaged, cognitive memory. Thus, I agree with Drs. Dieci and Guarnieri that this may be a partial explanation of some idiot savant abilities, particularly memory.

I cannot agree, however, that all savant abilities could be thus explained. While some of the calendar and lightning calculating or other numerical abilities could perhaps be reproduced by simple software programs, I have difficulty seeing how this is applicable to reproducing the more complex musical or artistic abilities, for example, that are so common among savants. Further, I cannot agree that simply lumping all of these abilities under the term "mental deficiency" in any way explains them. Also, such a grouping blurs the fact that savant abilities occur as frequently in early infantile autism as in mental retardation. While both mental retardation and early infantile autism are developmental disabilities, their etiologies, symptom complexes, and impairment of or sparing of intellect are sufficiently different to cause them to be viewed as separate entities.

Thus, using the term "mentally deficient savant" as an overall term would be as exclusionary and incorrect as using the term "autistic savant" to cover all cases. Not all autistic persons are savants and not all savants are autistic. Nor are they all "mentally deficient," as suggested by using that term to explain them. It is necessary to acknowledge that idiot savant abilities occur in both conditions. The term I prefer, "savant syndrome," is broad enough to encompass both those entities and I prefer it when referring to savants.

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DAROLD A. TREFFERT, M.D.
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Diagnosis and Classification of Erotomania

SIR: We dispute the conclusions reached by Jonathan H. Segal, M.D., in his article on erotomania (1). He stated that the major controversy surrounding erotomania is whether it ever exists separate from schizophrenia. He concluded that *DSM-III-R* is correct in classifying it under delusional disorder and that neuroleptics—only modestly effective and not

touching the core delusion—constitute the best medical treatment.

DSM-III-R and the literature agree that erotomania involves the delusion of being loved by another, usually of higher status. Unrelenting pursuit of the imagined lover is common. In most cases the patient is female, but forensic samples consist predominately of men, whose pursuit of the lover or misguided attempts to rescue her from imagined dangers result in arrests. *DSM-III-R* recognizes an association with affective syndromes but specifies that if the duration of the mood syndrome is not "brief," one can no longer diagnose erotomania, no matter how typical.

As with masked depression, in which somatic symptoms hide depressed affect, we believe erotomania can mask symptoms of mania by psychodynamically substituting for it. While mania defends against depression by denying depressing reality and substituting egomania and grandiose fantasy, in erotomania the patient derives heightened self-esteem from agrandizing the love object rather than the self.

Many reported cases suggest affective disorders. Raskin and Sullivan (2) concluded that erotomania serves the purpose of warding off depression and providing an outside source of nurturance following loss. Rudden et al. (3) described their case as resembling those of Seeman (4), which were intermittent, recurrent, and "cyclothymic." In a thoroughly researched review, Pope and Lipinski (5) concluded that the underdiagnosis of bipolar disorder was a serious contemporary problem. We agree. Just as catatonia occurs more often in bipolar disorder than in schizophrenia, we believe that erotomania occurs more often in bipolar disorder than in delusional disorder, and treatments effective for bipolar disorder should be used. From several successful cases, we present one that illustrates how such treatment allowed the patient to give up the core delusion.

Mr. A, age 34, had had 8 years of recurrent psychiatric hospitalizations, each after harassing a former grade-school classmate, even after she obtained a restraining order. One hospitalization occurred after he leapt on top of her outside her house to protect her from imaginary gunfire. His last admission began after another trespassing arrest. In jail he attempted suicide by putting his finger in an electrical socket. He complained of recurrent feelings of "weights on my head" and proclaimed himself a "master of self-defense." He insisted that the woman was in love with him, was sending him messages, and was his future wife.

He refused lithium and carbamazepine, which had been effective during past admissions, but accepted valproic acid. When this reached a serum level of 37 μg/ml, his grandiosity abated, and he became cooperative and developed insight. He no longer felt "weights" or heard the woman's voice, and within 10 days the erotomania began to diminish. He stated that the relationship "wasn't working out" and, because of her restraining order, she must not be interested in him. Under rigorous questioning he maintained that he was "through with her." At 4-month follow-up, he was still taking valproate and still believed that she no longer loved him.

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BRIAN E. WOOD, D.O.
RICHARD O. POE, M.D.
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Dr. Segal Replies

SIR: Drs. Wood and Poe raise several interesting points, but I see their case history as a useful addendum to, not a contradiction of, my conclusions. Their remarks notwithstanding, it is historically true that the major diagnostic controversies concerning erotomania have been 1) whether it ever exists as a distinct syndrome, rather than as merely one symptom of schizophrenia, and 2) whether it is a distinct syndrome or a subcategory of paranoia (now called delusional disorder). As I stated in my article, I believe that erotomania is best classified as a subtype of delusional disorder.

Regarding affective disorders, some cases of erotomania are accompanied by mild mood disturbances, and it is true that on occasion, manic patients have erotomanic delusions (although most of them certainly do not). It may be, as Drs. Wood and Poe assert, that bipolar disorder is underdiagnosed in general, and as they mention, it is true that erotomanic delusions can occur in the context of mania. However, this is a long way from concluding that, in general, erotomania masks symptoms of mania by psychodynamically substituting for them and that most cases of erotomania are actually cases of bipolar disorder. Whether the case of Mr. A was one of true erotomania or of bipolar disorder is difficult to discern, as Drs. Wood and Poe's description is not particularly detailed. Whether or not this patient was truly manic, however, the fact remains that there *is* a distinct group of persistently erotomanic patients, whose symptoms are stable and, unlike those of mania, last for years at a time and who show none of the other symptoms—insomnia, motor restlessness, pressure of speech, emotional lability, and financial impulsiveness—that are so typical of true mania. Such patients, in the absence of observable symptoms of mania or schizophrenia, are best diagnosed as suffering from delusional disorder, erotomanic type.

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Accuracy of Adults' Reports of Abuse in Childhood

SIR: At the risk of sounding like a broken record and once again being misunderstood, I feel compelled to comment on the titles of the articles by John Briere, Ph.D., and Lisa Y. Zaidi, Ph.D. (1) and Idee Winfield, Ph.D., and colleagues (2). The first article dealt with *reported* histories of sexual abuse in a psychiatric emergency room. The assertion was made that "substantial overreporting of abuse history in this sample seems unlikely." There were no data on the subjects studied which supported that contention, however. The second article dealt with *reports* of sexual assault in a community sample. Again, there were no corroborating, much less confirmatory, data.

The last time I suggested that there might sometimes be a difference between what is reported and what in fact happened (3), I was referred (4) to two articles that presumably refuted my suggestion with hard data (5, 6). In the first article it was asserted, "The majority of patients (74%) were able to obtain *confirmation* [italics mine] of the sexual abuse from another source." Details of the "corroborating evidence" were sketchy, however, and consisted of an unspecified amount of hearsay from other family members, apparently reported during group therapy. The second article referred specifically only to incest and included cases gathered in settings very different from a psychiatric hospital emergency room or therapy sessions.

I shall try again to make my concern clear. I am not naive about expecting "certainty" in a scientific article or anything else. I do think that those of us who write, review, and publish papers in this complex arena should be gravely concerned, however, about accuracy. I believe the only way we will ever untangle this difficult mystery is with clear definition of the variables, not a priori conclusions about the facts.

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Dr. Briere Replies

SIR: As recently as 1979, a chapter in the *Comprehensive Textbook of Psychiatry* reported the incidence of incest to be approximately 1 in 1,000,000 cases (1). Recent research, however, suggests that more than 30% of women in the general population and about half of female psychiatric outpatients report some form of sexual abuse in childhood (2, 3). As might be expected, these newer numbers bring with them some controversy, especially for those concerned about the honesty and/or reality testing of individuals who disclose childhood molestation. Dr. Rich's letter appears to reflect the thinking of this group: he questions the validity of patients' sexual abuse reports, bemoans the absence of "corroborating, much less confirmatory, data," refers to information from patients' family members as "hearsay," and cites studies such as that by Dr. Zaidi and myself as lacking sufficient concern for the accuracy of subjects' self-reports.

Possible distortion in patients' accounts of sexual abuse was briefly addressed in our article. We further indicated three reasons why we did not think that substantial overreporting was a major concern: 1) the abuse rate was comparable to the rates found in other recent clinical studies, 2) specific aspects of subjects' victimization correlated with

symptoms in ways that made intuitive sense and that had been reported by other authors, and 3) the clinical experience of the authors and others suggested that adults' disclosures of sexual abuse are typically accompanied by distress, shame, and fear of stigma, as opposed to obvious enjoyment of secondary gain.

More to the point, one must wonder why some of us are so suspicious of sexual abuse reports. In his distrust of self-report data, does Dr. Rich similarly discount patients' "uncorroborated" statements used in the psychodiagnostic process or in scoring psychological tests? At some point we must be willing to use the data available and to interpret them, with all due caution, as parsimoniously as possible. In the current instance, the example of Occam's razor would seem to dictate that we accept most adults' abuse reports as basically valid, rather than as being the result of complex psychodynamic processes that somehow motivate large numbers of individuals to either falsely report childhood injury for uncertain psychological reward or fantasize such experiences for their (rather unlikely) pleasurable aspects.

Finally, given that a large proportion of child abuse appears to go undocumented, it is not clear how we could accomplish the validation of sexual abuse histories that Dr. Rich desires—especially if one rules out family corroboration. Even if third-party corroboration were possible, however, the probable trauma to the subject that is inherent in investigating his or her early history (i.e., contacting and questioning relatives, neighbors, or friends) would preclude this option.

Despite Dr. Rich's supposition regarding our "a priori conclusions," the intent of the research he cites was to study a phenomenon of major importance, albeit with the flawed tools of retrospective/cross-sectional research designs. In the absence of data supporting reasonable alternative hypotheses, we deduce thus far that sexual abuse histories are common in clinical and nonclinical populations and are associated with significant negative sequelae.

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JOHN BRIERE, PH.D.
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The Power of Religion

SIR: Reading the article "Cults and Zealous Self-Help Movements: A Psychiatric Perspective" by Marc Galanter, M.D. (1) reminded me of an incident that occurred in our hospital.

While walking through the lobby, I came across a woman whom I recognized because I had treated her mother, Ms. A, 5 years earlier, during my psychiatric residency. Ms. A had had diagnoses of bipolar disorder and borderline personality disorder. During the time I treated her, her daughter was psychiatrically well. However, the daughter had subse-

quently developed a bipolar disorder similar to that of her mother and was now a patient in the hospital.

The daughter directed me to her room, where I was received cordially and affectionately by Ms. A, my former patient, who was visiting. She was wearing a button that announced, "I love Jesus." As I spoke to her, it was obvious that she had become deeply religious and had, in fact, been "saved." As a resident, I had been frustrated by Ms. A. She had needed to be psychiatrically hospitalized several times despite psychotherapy and treatment with lithium and thioridazine (Mellaril). I recalled asking my supervisor how to treat patients with borderline personality disorder, and he answered sardonically, "You refer them." As a trainee, however, that option was not available to me, so I persevered in her treatment. Now Ms. A revealed to me that since leaving therapy and putting her faith in the Lord, she had required no further hospitalizations. However, as I departed, she approached me and whispered, "I still take my Mellaril."

This heartening experience rekindled fonder memories of Ms. A. It also reminded me of other patients who had appeared to benefit more from commitment to religion than to medical psychotherapy. Although this may not be a revelation to clinicians whose practice integrates religion and psychiatry, it was a humbling experience for me. Nevertheless, Ms. A's parting words—her reference to the medication—also reminded me of sage advice from another supervisor, who made the following observation: "Remember, sometimes God heals through doctors."

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ARTHUR LAZARUS, M.D.
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Utilization of Partial Hospitalization Programs

SIR: In their article on partial hospitalization (1), Susanna Parker, M.D., and James L. Knoll III, M.D., stated that most psychiatrists have little training in a partial hospitalization setting. I believe that this statement is true. They also stated that most psychiatrists do not refer patients to partial hospitalization programs. I would take exception to this statement. We have an active partial hospitalization program at our Veterans Administration Medical Center. Not only are most of the referrals from other psychiatrists, we offer a 3-month rotation to our third-year psychiatry residents and a 6- to 12-month elective to our fourth-year residents. Our residents have shown a high level of interest, and it has become a sought-after rotation. My point is that lack of referral to partial hospitalization facilities may reflect lack of such programs or lack of awareness, rather than an overt bias against partial hospitalization.

I believe that partial hospitalization programs need to be expanded for two reasons. First, in this era of shrinking health care resources, partial hospitalization can cut down the cost of long-term psychiatric care. Second, it will improve the care of patients with chronic psychiatric illness. We are all aware of the problems psychiatrists have in the care of such patients (2). By taking an active role in teaching and training psychiatric residents how to treat chronic psychiatric patients, partial hospitalization programs can change these attitudes (3). Partial hospitalization may offer the best

combination of continued care and the potential for social rehabilitation.

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SURINDER SUCHA NAND, M.D.
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Drs. Knoll and Parker Reply

SIR: In response to the letter from Dr. Nand we make the following comments. We still stand by our statement that most psychiatrists do not refer patients to partial hospitalization programs. Obviously, Dr. Nand's hospital is an exception. It is an exception for two reasons. The first is that it is a Veterans Administration hospital, and the second is that it is part of a teaching program. We suspect that the economic and manpower factors inherent in that situation are the reasons for the high physician referral into that particular day hospital. From the review of the literature, we were not able to point to lack of awareness and lack of programs as major reasons for low referrals. We personally have been affiliated with a partial hospitalization program for more than 14 years in a major urban hospital with a university affiliation. We personally know that it is not lack of a program or lack of awareness that keeps referrals to a minimum.

While we certainly hope that an increase in use of day hospitals will cut down the cost of long-term psychiatric care, improve the care of patients with chronic psychiatric illness, and offer the best combination of continued care and the potential for social rehabilitation, it should be noted that day hospitals have been promising this since the Community Mental Health Act of the 1960s. Our article was not meant to look at any one particular factor or to continue fantasies of partial hospitalization's promises. Rather, it was to point out what is actually happening and to make an educated hypothesis about why partial hospitalization has not yet fulfilled its potential.

JAMES L. KNOLL III, M.D.
SUSANNA PARKER, M.D.
Dallas, Tex.

A Patient's View of Doctor-Patient Boundaries

SIR: I am a female patient currently (and for the past 4 years) undergoing intensive psychotherapy for major depression. I was led to read the article on doctor-patient boundaries by Thomas G. Gutheil, M.D. (1) as a result of a magazine article (2). Perhaps, as a patient's view, this letter may be of interest to some *Journal* readers.

My psychiatrist has what he calls "rules," which I have defined as "moving targets." The boundaries he has set between us seem flexible, and I often try to bend and stretch them. Sometimes he struggles with these boundaries, trying to balance his rules against his respect for me as a human

being. As I watch him struggle, I learn how to struggle with my own boundaries, not just the ones between him and me, but those between me and everyone I deal with in the real world. Sometimes my doctor throws up his hands in exasperation and even anger at me. Sometimes I have felt almost driven to suicide by frustration and rejection. But overriding all this, there seems to be a secure understanding that we each want what is right and comfortable for the other. We have not yet come to a complete consensus, except that 1) I am the patient, and 2) there is no sex. Here, I have no quarrel with Dr. Gutheil.

The rest of the boundary picture described by Dr. Gutheil, however, seems rather rigid to me (no "symbolic" gifts, even?). Dr. Gutheil's working sphere seems sterile and stagnant. In my view, the patient within such rigid boundaries learns to accept powerlessness in exchange for a supportive relationship. No wonder there is rage.

Dr. Gutheil was referring to "borderline" patients. I do not understand psychiatric illness classifications (the boundaries of which may also be blurry), but I find some similarities between what is described as borderline and my own condition. At the least, boundary problems seem relevant to any doctor-patient circumstance.

Presumptuously, I suggest that aspiring therapists be taught the same lessons that patients must learn, i.e., that caring and closeness between two people do not necessarily mean sex. For doctor and patient, in particular, some other way must be sought. The goal may never be reached, but the looking part is full of excitement and new knowledge if there is freedom to explore.

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2. Goode EE: The ultimate betrayal. US News and World Report, March 12, 1990, pp 63–64

ANN, A PATIENT

Dr. Gutheil Replies

SIR: The power of Ann's letter flows from just where she says it does: the *struggles* around boundaries. Indeed, as she so insightfully points out, rigid and mindless boundaries would produce a sterile and stagnant working sphere. But, clearly, Ann experiences a "secure understanding" with her therapist. Is there a better description anywhere for the holding environment so necessary in therapy? That is what good boundaries are intended to produce.

Ann's letter answers itself, from my perspective: the best boundaries are flexible and respect the human being; therapists' struggles with boundaries can model this for patients (and vice versa); caring and closeness need not mean sex; excitement, new knowledge, and freedom are not found in therapist-patient sex but in explorations.

This, indeed, is what therapists should be taught. However, the risk-management approach of my article precluded saying some things. I am delighted that Ann has said them.

THOMAS G. GUTHEIL, M.D.
Boston, Mass.

Perspectives on Psychiatry From Asian Cultures

SIR: Fumihiko Okada, M.D., in a letter to the Editor (1), lamented the lack of translation of papers on Japanese psychopathology written by Japanese psychiatrists, who consider themselves very indebted to occidental psychopathologists. He hopes that criticism from the West, for which they have expressed a need, will become possible through translated material published in a new Japanese journal of clinical psychiatry. Finding adequate translators is difficult.

A Japanese Mirror: Heroes and Villains of Japanese Culture by Ian Buruma (2) introduces us to a culture very different from ours. Buruma was born in the Netherlands in 1951. He is a producer, actor, and critic of theater, cinema, and television and has spent many years in Japan. His writing will be fascinating to psychiatrists interested in varieties of sexual and cultural development. Anyone interested in what the Japanese believe they are, as well as the conflict between this and what they would like to be, may find many examples. The attitude toward women as she-devils and goddesses and men as heroes, gangsters, or ridiculous persons leads to many complexities, shown in the history of theater, movies, television, and comic magazines. The wealth of detail cannot be easily summarized but should be digested to help us view the contrasting conflicts between Japan and the larger scene of China and the newer, smaller scene of our own culture, where we may not admit the motes in our eyes as easily as we see them in others'.

As a background to these works, there is the contrasted writing of Roberto Ong, a psychiatrist from the Philippines interested in linguistics, whose valuable English summary of Chinese attitudes toward dreams, *The Interpretations of Dreams in Ancient China* (3), is very worth reading. None of the previous 22 volumes of this series on China has been translated into English. In one chapter Ong discusses the history of Chinese philosophers' attitudes toward the dream of the philosopher who awoke from dreaming that he was a butterfly and wondered how he could tell that he was not now a butterfly dreaming that he was a man. The authors left this question open-ended, just as some of us still may be open-minded in sharing this enigma with patients who complain of not being able to tolerate such complexity and want a quick resolution!

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DR. W. CLIFFORD M. SCOTT
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Reprints of letters to the Editor are not available.

Correction

In the article "Sertraline in Obsessive-Compulsive Disorder: A Double-Blind Comparison With Placebo," by Michael A. Jenike, M.D., et al. (July 1990 issue, pp. 923–928), there are a number of errors that resulted from incorrect computer entry of the randomization code.

The final conclusions of the study are not changed, but a stronger trend toward usefulness of the drug is exhibited. In view of positive data from the multicenter trial of sertraline of which this was one center (G. Chouinard, W. Goodman, J. Greist, et al.: Results of a double-blind placebo controlled trial using a new serotonin uptake inhibitor, sertraline, in obsessive-compulsive disorder. Psychopharmacol Bull [in press]), it is likely that the nonsignificant differences from placebo are due to small sample size.

Patients in the placebo and sertraline groups were still similar in clinical characteristics (table 1 in the original paper), and there were few side effects in either group (table 2). The corrected table 3 below summarizes the corrected data analyses, which were done by means of analysis of covariance. All comparisons were nonsignificant beyond p>0.10. On the Yale-Brown scale, the Maudsley questionnaire, and the global scale, the interaction effect was nonsignificant, so main effects can be unambiguously interpreted. On the NIMH scale, the interaction effect was significant, so main effects could not be unambiguously interpreted; thus, tests of simple main effects were carried out between drug and placebo at each of the five trials. None of the resuls of the tests of simple main effects was significant (all p>0.10).

Also, to clarify a point in the paper, the new drug application requesting that obsessive-compulsive disorder be included as an indication for sertraline will not be submitted for some time, but an application was filed for depression as an indication in 1988 (personal communication, Pfizer Pharmaceutical Company).

MICHAEL A. JENIKE, M.D.
LEE BAER, PH.D.

Table 3. Baseline and Posttreatment Scores on Measures of Obsessive-Compulsive Symptoms for Patients Treated With Sertraline (N=10) or Placebo (N=9)

Time and Treatment	Yale-Brown Scale		NIMH Scale		Global Assessment		Maudsley Questionnaire	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline								
Drug	23.4	5.0	9.5	1.2	5.1	0.6	15.8	5.5
Placebo	22.1	5.8	8.4	1.4	4.7	0.7	14.9	3.0
Week 2								
Drug	23.0	5.1	9.2	1.5	5.1	0.7	—	—
Placebo	21.7	5.1	8.3	1.3	4.6	0.9	—	—
Week 4								
Drug	22.7	5.8	9.1	1.7	4.8	0.9	—	—
Placebo	23.7	6.5	8.7	1.6	4.4	0.9	—	—
Week 6								
Drug	21.6	7.1	9.2	2.1	4.8	0.9	—	—
Placebo	22.0	6.3	8.4	1.4	4.6	0.9	—	—
Week 8								
Drug	20.6	7.3	8.5	2.1	4.6	1.1	—	—
Placebo	21.7	7.2	7.9	1.5	4.2	0.7	—	—
Week 10								
Drug	19.4	8.5	8.3	2.4	4.5	1.4	14.2	5.6
Placebo	23.7	8.1	9.2	2.2	4.7	0.7	15.2	4.7

Annual Reports to the Membership

The following are edited versions of the annual reports by the APA Secretary, Treasurer, Medical Director, Speaker, Speaker-Elect, and the chairpersons of the APA Committee on Constitution and Bylaws, Committee on Membership, and Committee of Tellers. The reports were presented at the APA annual business meeting in New York on May 14, 1990.

Report of the Secretary: Summary of Actions of the Board of Trustees, May 1989–May 1990

Philip M. Margolis, M.D.

OVERVIEW

It is my personal and Constitutional privilege as Secretary to report to the membership the actions taken by the Board of Trustees and some of the significant activities of the Association over the past year. The actions reported do not include a number of issues referred to appropriate components for further study and recommendation. As required by our Constitution, especially important issues will be discussed and clarified at the annual business meeting and a full report will be published in the *American Journal of Psychiatry*.

The work of the Association has proceeded at a rapid pace over the past year. Major concerns have been quality assurance, managed care systems, practice parameters, membership, ethics, judicial activities, legal issues, and finances. In addition to regularly scheduled reports from the Assembly, Joint Reference Committee, and other components, members of the Board have contributed significantly to the development of the Board's agendas for the meetings in June, September, and December 1989 and March 1990. A portion of each meeting was spent discussing policy issues and developing strategies to enhance the field of psychiatry and to assist members, patients, and their families. New directions have been given to some existing components, and the Board has continued or established ad hoc committees to address major issues. Of particular note is the new Council on Addiction Psychiatry, which will begin work this year. The new Task Force on the Homeless Mentally Ill began to work with related components in 1989.

Membership

As of Jan. 1, 1990, the membership was 36,208, which indicates a net gain of 1,040 members during 1989, or a 3% increase. The net gain in membership during 1989 exceeded the net increases during 1987 and 1988 (1,013 and 862, respectively). Of the new members enrolled in 1989, 316 were Medical Student Members and 1,357 were Members-in-Training, or 87% of the new enrollments. Members-in-Training continue to be the greatest source of General Members.

Residents are significantly involved in the activities and components of the Association and include a voting Member-in-Training Trustee and nonvoting Member-in-Training Trustee-Elect on the Board of Trustees and an area representative and deputy representative in each of the seven area councils. The Committee of Residents and Fellows and the resident fellowship programs continue to have representation on the Board. The Committee of Young Psychiatrists is a relatively new component that is charged to identify these APA members, to assess their interests and needs, and to make recommendations as to how the Association can best serve them. The committee is extensively involved in the activities of the American Medical Association (AMA) Section Council on Psychiatry and sends a delegate and an alternate to the annual and interim meetings of the AMA Young Physicians Section. In addition, APA has a young physician delegate and alternate delegate in the AMA House of Delegates.

Membership and Fiscal Policies

There has been growing concern about national and district branch dues and the formulas by which they are determined. Issues of concern include 1) the wide variation in dues among the district branches (some district branch dues are higher than the national dues), 2) the growing number of members who hold dues-exempt status, even though they are at peak earning levels, and 3) the retention of younger members, who may have problems in paying the local and national dues because they are paying off debts for their education and have lower incomes.

The present criterion for dues-exempt status as a Life Member or Life Fellow is the "rule of 95," i.e., the sum of a member's age and years of active membership must equal 95; this formula was established by a vote of the membership in 1979. Of the total membership, 28,370 members are billed for national dues. It is time to reexamine the criterion for dues-exempt status. It is fortunate that many members are living longer, more vigorous lives and continuing in active practice, but a significant number of members are reaching dues-exempt status now, and this number will increase in the future because members are joining at a younger age. District branches are particularly affected, and this also has an impact on the national income. In the past, both the Assembly and the Board have agreed that national dues should be increased by relatively small increments

each year rather than by periodic larger increases. For the most part, national dues have approximately kept pace with the inflation rate in the national economy, but other internal and external factors beyond APA's control affect the need for dues income.

In November 1989, after a dues increase approved by the Board in September, an Assembly action paper recommended that APA freeze member dues at the 1990 level for 1 year while the budgeting process is restructured. The Constitutional and Assembly membership committees discussed the paper with the authors and developed an alternative proposal, for establishing an ad hoc committee to conduct an intensive, rapid study of many related issues. In December 1989, the Board established the Ad Hoc Committee on Membership and Fiscal Policies, which includes representation from the Board and Assembly. The committee is studying a wide range of past and current membership data and is making projections for the future; a senior staff consultant with expertise in fiscal and actuarial matters was hired to assist the committee.

Discussions in various settings, including the Assembly, have suggested amending the APA Constitution and Bylaws to uncouple Life status from dues; this ultimately would require a vote by the membership. Ways to honor members who have reached Life status could be developed. More difficult issues include development of appropriate modifications to the dues structure and a transition plan; dues-exempt status might be available only to members aged 65 or older, and graduated dues for younger members might be initiated. The ad hoc committee is making recommendations to the Assembly in May and to the Board in June.

A preliminary report of the Joint Board and Assembly Ad Hoc Committee on Membership and Fiscal Policies indicated that total APA membership will grow more slowly in the next 10–25 years. APA will be getting fewer members from residents' ranks, and the number of older members is increasing. We need to think of raising dues more modestly; currently both national and district branch dues are moving considerably ahead of inflation. These high dues may be causing defections. The district branches *are* the membership, the life blood of APA, and need to participate in "dues reform." We await the final report of this committee with interest; it may have found a way to accomplish both relief from dues and legitimate increases. For example, a formula may be devised to hold increases to or near the rate of inflation.

Member Benefits

The APA professional liability insurance program is highly valued by many members and continues to be well subscribed. The May 1, 1990, renewal is in progress, and there are no rate increases in any area and rate decreases in many of them. The process for renewal has been improved over the past 2 years; applications are preprinted and letters of explanation accompany the necessary legally worded notices of renewal or expiration. While the program continues to be comprehensive and competitive, the APA Board Committee on Insurance, the Risk Management Committee on the APA Insurance Trust, and the board of directors of the Psychiatrists' Mutual Insurance Company continue to look for ways to improve the coverages and to make this program even more valuable to the membership.

In response to requests for additional insurance and on the recommendation of the Board Committee on Insurance, in March 1990 the Board authorized offering excess coverage to holders of APA-sponsored professional liability insurance (except in New York because of that state's requirements). Also in March, the Board authorized offering a medical defense policy to members who have APA professional liability insurance or who receive coverage through their institutions and do not purchase liability coverage on the general market.

The legal consultation plan offered to APA members continues to be very well received, and participation has increased 13% over last year. The APA Committee on Special Benefit Programs also offers a risk management seminar, "Law in the Practice of Psychiatry," and this fall will implement a "Career Choices in Psychiatry" seminar designed for residents. A membership retirement plan was approved by the Board of Trustees in March; when contractual arrangements are complete, the plan will be publicized to the entire membership. The Committee on Special Benefit Programs is developing new pro-

grams for the consideration of the Board, which include Member Communications Plus (discounted facsimile machines, cellular telephones, and other office equipment), a vacation travel program, and new seminars to meet the changing needs of psychiatrists.

After months of consideration and planning, the APA Committee on Member Life, Accident, and Health Insurance recommended restructuring the APA medical insurance plan; this change was approved by the Board in December 1989 and implemented on Jan. 1, 1990. The new plan offers protection from catastrophic medical expenses. The long-term disability plan was improved and was effective Feb. 1, 1990. The maximum benefit on the plans with 90-day and 180-day waiting periods was raised from $5,000 to $7,500.

Professional Risk Management Services, Inc. (PRMS) is the professional management company for APA's professional liability insurance program, as well as other member benefit programs. APA was one of the original investors in PRMS but sold its holdings in PRMS this year. APA continues to control the APA Insurance Trust, Psychiatrists' Mutual Insurance Company, and the Risk Management Committee on the APA Insurance Trust and to contract with PRMS for services.

Quality Assurance

The Ad Hoc Committee to Evaluate Quality Assurance Activities reported to the Board in June, September, and December 1989. This committee, with representation from the Board and Assembly, was charged to assess the current state of quality assurance activities in psychiatry and APA's efforts in this arena and to develop a series of proposals and actions relative to APA's future efforts. While APA was involved in negotiations for a new CHAMPUS contract for utilization review and case management for military personnel and their dependents, it was necessary to hold some of the Board's discussions in executive session. Appropriate actions were reported after each Board meeting, and full reports were made to the membership and the Assembly once APA learned that another organization had been awarded the CHAMPUS contract. Another ad hoc committee was appointed to assist the Medical Director and staff in closing down all of APA's commercial utilization review projects. APA remained dedicated to helping members deal with the transition of the CHAMPUS contract and helping staff in the Office of Quality Assurance obtain other positions. These ad hoc committees were discharged with appreciation in March 1990.

Given these changes, the Board recognized that APA would need a component on quality assurance activities with a focus and set of responsibilities very different from those assumed by the current committee. In March 1990, the Board voted to discharge, at the close of the 1990 APA annual meeting, the current committee and to establish a new committee. The Council on Economic Affairs was assigned responsibility for developing a charge for the new committee.

Government Affairs

The Joint Commission on Government Relations and the Division of Government Relations sponsor a biennial state or federal legislative institute. In early February, the 1990 State Legislative Seminar was held in Dana Point, Calif. Attracting the largest audience ever, the seminar was attended by over 130 members and staff from more than 60 district branches. In addition to timely panel discussions on such important issues as Oregon's health care rationing plan, psychologists' prescribing and hospital admission privileges, and utilization review, the seminar included keynote addresses by state and federal legislative leaders from across the country. Among them were John L. Martin, Speaker of the Maine House of Representatives and incoming president of the influential National Conference of State Legislatures; Paul "Bud" Burke, state senator from Kansas; Tarky Lombardi, Chairman, New York Senate Finance Committee; and U.S. Senator Pete Wilson from California. A highlight of the seminar was the presentation of the Jacob K. Javits Public Service Award to North Carolina state senator Kenneth Royall, Jr., for his 20 years of legislative leadership and commitment to mental health. Senator Javits's widow, Ms. Marian Javits, and his daughter, Ms. Carla Javits, participated in the award presentation.

The Board took a number of actions with respect to the Kennedy-

Waxman legislation on minimum health insurance benefits. As originally introduced, this bill specifically excluded coverage for patients with mental disorders, but the bill was amended in the Senate Labor and Human Resources Committee. The amended legislation included a mental health benefit essentially comparable to most states' psychotherapy benefits (i.e., 20 outpatient visits at 50% copayment and 45 days of inpatient care per year) without regard to self-insurance exemptions and limited impact on small group coverage. The amended legislation also included nondiscriminatory psychiatric medical management of patients. The actions of the Board represented the discussion and concern within the Association about the various limitations of the bill and the potential impact on states that have higher levels of mandated coverage than provided by the bill. This legislation was reintroduced in the 101st Congress and reported out of the Labor and Human Resources Committee as previously described; it awaits Senate floor action. There has been no comparable movement in the House of Representatives, where it awaits further hearings. Since the introduction of the Kennedy-Waxman bill, legislation dealing with national or universal health insurance has been introduced. A small work group with representation from the Board and Assembly and the Joint Commission on Government Relations will report to the Board in June with recommendations as to how APA should address national or universal health insurance in the future.

I will briefly highlight some of the many successful lobbying activities APA conducted during the first session of the 101st Congress. Last year we achieved the first major change in Medicare's psychiatric benefit in 22 years: in essence, a quadrupling of the psychotherapy benefit to $2,200 with a 50% patient copayment and a nondiscriminatory medication management cap with a 20% copayment. Since then, Medicare's discriminatory dollar limitation for outpatient mental health services was eliminated entirely, thus providing a nondiscriminatory mental health benefit. Also, APA was successful in amending legislation that would allow direct reimbursement of psychologists and social workers under Medicare; the amendment requires consultation with a physician about potential medical problems. Despite continued federal budgetary deficits, APA was again successful in obtaining significant increases in the research budget for the National Institute of Mental Health (NIMH) and other institutes under the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), obtaining an increase higher than the inflation rate in each of the past 2 years. In both fiscal years, the percentage increases exceeded those of the National Institutes of Health, and the fiscal year 1990 increase obtained by NIMH was the highest ever.

The Corporation for the Advancement of Psychiatry's political action committee (CAP/PAC) has been playing a key role by supporting House and Senate incumbents and challengers who are sympathetic to the concerns of psychiatry. Meetings were held with candidates who are running for the 24 open seats in the House and Senate to influence them and sensitize them to our concerns for the mentally ill. Since defeat of an incumbent is uncommon, CAP/PAC tends to support incumbents; however, we support a challenger if we feel that person will take a more active role in our efforts than the incumbent. To date, CAP/PAC has contributed to the campaigns of 76 incumbents and four challengers. In 1989, CAP/PAC was involved in special elections that produced such winners as Congresswoman Jill Long (D-Ind.), Congressman Gary Condit (D-Calif.), and Congressman Gene Taylor (D-Miss.).

Economic Affairs and Practice Issues

Managed care. In December 1989, the Board established the Ad Hoc Committee on Managed Care Issues to delineate potential forms of assistance to district branches, members, and patients for coping with the demands of third-party reviewers and managed care programs. The committee has representation from the Board, Assembly, and appropriate other components. In addition, the Board allocated up to $50,000 in the fiscal year 1990 budget to investigate legal issues involving managed care and to develop economic data on mental health and substance abuse services.

The ad hoc committee met in January and February 1990 and identified a number of steps that can be taken rapidly, including

development of a central information clearinghouse and a network in the district branches to identify local problems and the strategies being used to resolve them. Model legislation has been developed; this model, together with background material, is being sent to the district branches and the Assembly to assist in their discussions of these issues. It is important for all of us to realize that managed care is here to stay and that we must learn how to use it to the best advantage for our patients. Some managed care systems are better than others, but a common goal is cost containment. There is a tenuous relationship between psychiatry as a profession and proprietary organizations, but we will find ways to educate the leadership in the managed care industry about the efficacy of psychiatric treatment and to involve them in the work of APA components.

Practice parameters. There is growing recognition that the psychiatric profession must develop practice parameters and standards of care before others do so. The AMA has formed a partnership with the medical specialty societies to facilitate the development of practice parameters. APA continues to participate in this partnership. APA's publication of *Treatments of Psychiatric Disorders* (1) and the new report of the Task Force on Electroconvulsive Therapy (2) have initiated the development of practice parameters for psychiatry. However, development of practice parameters is a long, complex, and expensive task. They need to reflect the state of the art and be acceptable to practitioners. Any APA process will be open, will be well documented, and will involve clinical practitioners. Although practice parameters are related to quality assurance standards, the two are separate and distinct. In March 1990, the Board established the Joint Board and Assembly Work Group on Practice Parameters to address these issues and make recommendations about APA's role in the future.

Codes and reimbursements and the relative value scale. The Work Group on Codes and Reimbursements and the Work Group on the Harvard Resource-Based Relative Value Scale (RBRVS) Study were very active over the past year and will continue to work together on overlapping issues. While the editorial board for the AMA's *Current Procedural Terminology, 4th edition (CPT-4)* did not accept all of the codes and descriptors proposed by APA in 1989, the AMA did endorse some of them. *CPT-4* includes 1) new codes for medical psychoanalysis and family medical psychotherapy (without the patient), 2) a change in the wording for "pharmacologic management" so that it better describes psychiatric practice, 3) cross-references in the psychiatry section to three new or expanded entries for telephone consultation, and 4) some minor editorial changes. The editorial board delayed action on other recommendations for several reasons, including a perception that some of the revisions needed further study. Also, the AMA has unofficially endorsed some of APA's proposed codes and descriptors, and they can be used in refining the earlier Harvard study. Five members of the Harvard study group also are members of APA's work group. APA continues to press for a seat for a psychiatrist on the editorial board.

There is inconsistency in the local implementation of the CPT codes for psychiatry by Medicare carriers. The U.S. Health Care Financing Administration does not issue nationwide regulations, so the states have great latitude in interpreting the national guidelines. For example, some states permit reimbursement for only one psychiatric procedure per day, while others allow several, as appropriate. The Assembly Executive Committee has been asked to look at ways to mobilize the Assembly and the district branches to gather information about local problems and the strategies being used to solve or ameliorate them, so data can be shared and the same strategies used elsewhere if desired.

The work group on the RBRVS has continued to examine all forms of physician payment reform using an RBRVS. At the end of its last session, Congress passed legislation requiring Medicare to pay physicians on the basis of an RBRVS. Since psychiatry is currently being resurveyed, the impact on psychiatry is still unknown. A subgroup composed of members from the RBRVS and coding work groups developed some potential levels of service for codes and vignettes for the resurvey. In addition, the work group on the RBRVS has attempted to identify aspects of the RBRVS that need further refinement. The subgroup reviewed all of the comments from a number of APA components and delineated critical aspects of patient care for inclusion in the vignettes. This review was well received by

the principal investigator for the Physician Payment Relative Value Study.

Joint Commission on Accreditation of Healthcare Organizations (JCAHO). APA's representative and staff have been participating actively with the JCAHO over the last year. In March 1990, Medical Director Dr. Melvin Sabshin reported that the JCAHO had agreed to some important changes in its methods for surveying psychiatric hospitals and in the composition and training of the surveyors. Also in March, the Board discussed standards for admission to a hospital. The Board voted that APA should recommend to the JCAHO that it require each hospital to have standards for admission, which would be written by the hospital and would be examined before accreditation. The Assembly is discussing this matter during the May meetings.

Marketing manual for district branches. In December 1989, the Board approved a marketing manual as a resource for district branches; it is currently available from the Office of Economic Affairs. Each district branch received a complimentary copy early in January 1990. The manual contains information on developments in the health care industry and their impact on psychiatry, on marketing research, and on marketing to employers, unions, and managed care organizations; it also contains a glossary of health care financing terms. In addition, the manual provides a framework for initiating a marketing program (planning and budgeting, selecting target markets, determining a time frame, and developing a strategy).

Through the Office of Economic Affairs, APA provides technical assistance related to health care financing, e.g., managed care and marketing, to district branches. This office continues to monitor and affect developments in the private health insurance industry. A meeting was held for representatives of the nation's premiere benefits consulting firms and members of the APA leadership, and staff is surveying private insurers to ascertain their policies regarding denial of coverage for preexisting conditions. The data in *The Coverage Catalog* (3) were updated in 1989, and *Economic Fact Book for Psychiatry* (4) will be updated in 1990.

A toll-free Medicare inquiry line is undergoing expansion and will become the Medicare/Managed Care/Utilization Review Information Service. In addition to answering immediate questions, the service will facilitate research, trend analysis, and dissemination of information to specific sources. Additional information is provided by the Office of Economic Affairs in *Eco-Facts*, a quarterly newsletter on the economics of psychiatric practice, as well as by staff on an individual basis and at conferences.

Resource Development

The Board has established the "Fund for the Future—APA," which allows special charitable initiatives that go beyond APA's regular dues-supported programs. The Fund for the Future—APA is a key element of the overall strategic plan for APA fund-raising. Its features include a tribute program to promote recognition of colleagues, friends, and others through contributions, as well as a newly created pooled income fund. The program is being publicized in *Psychiatric News* and district branch newsletters. As part of a pilot study, letters of solicitation were mailed in March 1990 to 353 selected APA members.

Ethics

New procedures for handling complaints of unethical conduct were developed in concert with the Ethics Committee, the district branches, and the Assembly, and they were approved by the Board in June 1989 for implementation on Oct. 14, 1989. The new APA procedures include all of the procedures specified in the Health Care Quality Improvement Act of 1986. This act provides immunity for peer review actions if certain requirements are met. The Ethics Committee held a workshop in November 1989 for chairpersons of district branch ethics committees and will continue to provide additional educational material and seminars to assist the district branches with implementation of the new procedures. Also, the Board has allocated up to $50,000 in the 1990 budget for legal and staff assistance to the district branches. In March 1990, the Board asked the Assembly to review criteria for distribution of this financial aid to district branches, with the understanding that the criteria would be used administratively in the interim to respond to requests. While some have expressed concern that the new procedures will be more costly, the Ethics Committee believes they will be cost-effective in the long run, for instance, by avoiding defense costs associated with suits in the past. In addition to the activities of the Constitutional Ethics Committee, an Assembly task force is interacting with the district branches.

In March 1988, the Board voted to indemnify district branches against legal expenses and/or damages not otherwise covered by insurance that are incurred in suits based on actions related to ethics complaints, under specified circumstances; in March 1990, the Board voted to extend this coverage to individual members of the district branches and their staffs for their ethics activities.

The actions of the Board last year included changes in annotations regarding sexual involvement between faculty members or supervisors and trainees or students and an annotation on sexual involvement with one's former patients.

Judicial Affairs

APA has been involved separately and with other organizations in a number of judicial cases during the past year. A wide range of issues have been addressed, including reproductive choice, restrictive disability standards for children as applied by the Social Security Administration, confidentiality of a patient's psychiatric treatment records, and whether a mentally incompetent prisoner may be medicated with psychotropic drugs to restore competency for execution. APA continues to await the outcome of an appeal in *CAPP v. Rank*, a California case concerning hospital admitting privileges for psychologists. The case was argued on April 9, 1990; a decision must follow within 90 days. [Shortly before press time APA learned that the appeal lost in a 4-3 vote. Ramifications of this decision and possible next steps will be thoroughly explored.] The Board extended its deep appreciation to Paul Appelbaum, M.D., who has served as chairperson of APA's Commission on Judicial Action since 1984.

Research

In concert with the Assembly, the Board approved a position statement about the use of animals in research, and a number of APA components were involved in informing the public about the need to use animals in research. Ms. Frankie Trull, president of the Foundation for Biomedical Research, met with the Board in September 1989 to discuss these important activities. The Council on Research and the Office of Research have been very active during the past year.

The development of *DSM-IV* is an open process that provides many opportunities for comments and suggestions from a variety of sources. The Assembly is represented on the Task Force on DSM-IV and on the oversight components, including the Committee on Psychiatric Diagnosis and Assessment and the Council on Research. Work groups to address specific disorders have completed a search of the literature, and initial drafts of their reviews will be circulated to advisors for comment. Copies of the *DSM-IV Update* newsletter are circulated periodically to the Board, Assembly, components, and interested individuals. Anyone with comments or suggestions on any aspect of *DSM-IV* is encouraged to contact the APA Office of Research in Washington, D.C.

AIDS

In June 1989, APA cosponsored the AMA's "International HIV Conference: Counseling, Testing, and Early Care," which took place just before the Fifth International Conference on AIDS in Montreal. The Board has authorized APA's participation as a cosponsor for the 1990 AMA international HIV conference, to be held in San Francisco on June 19, 1990, in conjunction with the Sixth International Conference on AIDS.

As recommended by the Commission on AIDS, the Board approved in September and the Assembly approved in November 1989 the "Position Statement Opposing Mandatory Name Reporting of

HIV-Seropositive Individuals," which was published in the April 1990 issue of the *American Journal of Psychiatry* (5). In September 1989, the Board authorized the commission to seek outside funding to produce and distribute the "AIDS Primer," at no cost, to all residents in psychiatry, psychiatric residency training directors, and department chairpersons. When funds become available, *Psychiatric News* will announce the availability of the "AIDS Primer" and all district branches will be informed by mail. In September 1989, the Board authorized APA to contact the American Board of Psychiatry and Neurology (ABPN), the National Board of Examiners, the Accreditation Council for Graduate Medical Education, and the Residency Review Committee for Psychiatry to request that they consider increasing HIV content in their psychiatry and behavioral sciences curricula and examinations. Letters were written to these organizations in October 1989.

Homeless Mentally Ill

In concert with other APA components, a task force was established to address the needs of this growing population. In March 1990, the Board accepted an interim task force report, "General Directions for Public Policy in Behalf of the Mentally Ill Among the Homeless Population." The statement was adopted for appropriate use by APA to further psychiatry's involvement in relevant federal, state, and community activities. To assist members in their local activities, brochures can be obtained by writing to the APA Division of Public Affairs. APA is participating with the American Bar Association in a project to assist the homeless mentally ill who also have legal problems.

Public Affairs

Over the past year, the Division of Public Affairs accelerated its efforts to bring positive messages about mental illness and psychiatric diagnosis and treatment to the attention of the general public, APA members, other mental health professionals, and other physicians, both at the national and local levels. Our activities are grouped under the banner of our multiyear "Let's Talk About Mental Illness" campaign, which includes Mental Illness Awareness Week. This was the first year in which we developed and marketed the campaign as a 12-month activity. The purpose of the campaign is to raise public awareness of mental illness and the effectiveness of psychiatric diagnosis and treatment through a steady flow of public information, materials, and activities from many sources to many audiences over an extended period of time. We have, whenever feasible, linked all of our divisional activities to this campaign in order to coordinate our efforts, set priorities, and maintain our focus on the ultimate objective of increased public awareness. We believe that by taking this long-term approach we can best serve the public information needs of psychiatry as a profession. The public image of the profession is inextricably tied to public perceptions of mental illness.

International Activities

In June and September 1989, the Board discussed recommendations from the Council on International Affairs to prepare for the World Congress of Psychiatry, which was held Oct. 12–19, 1989, in Athens. During that meeting, the World Psychiatric Association (WPA) accepted new statutes and bylaws that created a new eight-member Executive Committee, to which two APA members were elected. New regulations also provide for meetings of the General Assembly every 3 years, rather than every 6 years. A slightly amended voting structure was adopted to give more voting power to the smaller organizations, and the Committee to Review Abuses of Psychiatry was strengthened. During the congress, there was considerable debate about the possible admission of the official Soviet psychiatric organization, the All Union Society of Psychiatrists and Narcologists of the USSR. Following public acknowledgment that previous political conditions in the U.S.S.R. created an environment in which psychiatric abuses occurred for nonmedical reasons, and promises to improve conditions in the future, the All Union Society was accepted into membership with the following condition: "A site

visit by the WPA Review Committee will be made in one year; if its report indicates that psychiatric abuse continues, a special session of the WPA General Assembly will be convened to consider suspension of the All Union Society."

In March 1990, Dr. Johannes Meyer-Lindenberg flew from Germany to discuss problems with the scheduling of the APA joint meeting with the German Society of Psychiatry and Nervous Diseases. He and Dr. Eric Plaut, chairperson of the APA Task Force to Plan the Joint Meeting in Germany in 1990, discussed several options with the Board, including canceling the joint meeting or rescheduling it for later in October 1990. After lengthy discussion, the Board voted to join the German Society of Psychiatry and Nervous Diseases in extending an apology to all people who had experienced hurt from the scheduling of the joint meeting during Yom Kippur and, further, voted to revise the meeting schedule so that no part of the program or associated travel time would occur during Yom Kippur. APA's Office of International Affairs took steps immediately to publicize the change in dates and sites in Germany.

Internal and External Liaison

Internal communication with the district branches has become increasingly important. The district branches gather information about major economic issues and have considerable leadership and expertise to share with the national organization and with each other. Each fall and during the annual meeting, the district branch presidents-elect are convened to discuss mutual concerns and to learn how the national elected leaders and staff can assist them. Almost 60 of the 76 district branches have paid staff, whose wide range of expertise enhances local functioning and improves interactions with the national association. Many of these staff members attend the fall orientation and annual meetings. The forum "Directions in Insurance Coverage for Psychiatric Services" was held for district branch presidents-elect and staffs in conjunction with the Assembly meeting in November 1989; the panelists were psychiatrists who held key positions in the insurance industry, who were involved in national health policy studies, or who were coping with managed care systems in a variety of settings, including private practice.

Several district branches responded well to natural disasters, such as Hurricane Hugo and the San Francisco earthquake, and were assisted in a variety of ways by the Central Office staff. A new task force has been established to study the psychiatric implications of such disasters and to recommend mechanisms for providing financial and other assistance. Also, the task force was asked to make recommendations about ways to honor and commend district branches and individuals for heroic efforts during disasters.

There is a growing number of members who focus their practice in one or more areas, and some of them belong to related psychiatric organizations with special focuses. We are exploring ways to use the expertise of these members in the work of the Association and to give them a greater voice in policy development. Representatives from over a dozen allied organizations met with the Ad Hoc Committee on Liaison Activities in September 1989 to discuss existing and potential avenues for access to APA and to identify services that APA could provide or sell to some of these organizations.

The Ad Hoc Committee on Subspecialization has been studying ways in which individuals receive recognition for their special expertise, and it has developed recommendations for criteria, procedures, and a governance structure by which APA could evaluate requests from groups seeking added qualifications beyond certification in general or child and adolescent psychiatry. The ad hoc committee, after wide discussion in the Assembly and the councils and components, assisted the Board in making recommendations to the ABPN about added qualifications in geriatric psychiatry. The ABPN recently informed the APA Board that the first such examination is scheduled for April 1991. The ad hoc committee also had a preliminary discussion of the potential impact of accreditation of fellowship training programs on subspecialization, and it recommended that examination of this issue be part of a charge to a new component to replace the ad hoc committee.

The Joint Reference Committee and the Assembly Executive Committee held a second joint meeting in February 1990. Coping with

managed care systems and APA's role in developing practice standards were key in their discussions.

Closing Remarks

Of the many things happening in APA, I would like to highlight six.

1. Economic issues. Our health care system is worrisome and in trouble. APA has terminated its formal review activities involving quality assurance. One advantage of this is that we are developing a number of other approaches to assist our members (such as an 800 line), rather than placing ourselves at times in an adversarial position toward them.

The development of practice parameters and standards of practice and care is a thoughtful and useful project. In this effort we are working with other organizations, such as the AMA. In fact, practice parameters will be shaped inside and outside APA. For example, the Board and Assembly work group and the Council on Research combine their efforts.

The trouble with managed care is that it is not being directed by psychiatrists. Certainly many see managed care as a threat to our autonomy and effectiveness. Practice parameters may help here, e.g., to assure quality of care while others are preoccupied with cost-effectiveness (cost containment). Unfortunately, cost-effectiveness mostly means dollar reduction. As has been noted, we clinicians have to spend our time justifying care, rather than providing it. A new ad hoc committee on managed care issues has been established. It is likely that we need to reform managed care rather than obliterate it; it is probably here to stay.

2. Ethical issues. I am delighted that Dr. Manuel Garcia developed a position statement on stigma as a political tactic. Very recently the Board and Assembly approved a statement denouncing the use and abuse of mental illness/emotional problems as a way of demeaning the opposition candidate in an election campaign.

We have developed new ethics procedures and have streamlined old ones, which are tough but workable. We hope that these will provide some uniformity to the procedures while preserving flexibility. The ethics workshop was a big success. The Board has allocated up to $50,000 to provide legal and other assistance to district branches.

3. Psychologists' prescription and hospital privileges. The battle goes on, punctuated by appropriate negotiations. The *Capp v. Rank* decision will soon be made. [At press time it had been made, against the interests of APA.]

4. Social-political conscience. We have a task force for the homeless. There is a new council on addictions. We are thinking of how best to be helpful to Soviet psychiatry. Dr. Pardes has been an activist President, as his stand on, for instance, animal research testifies. He has confirmed that psychiatrists have much to offer in developing, shaping, and challenging the social conscience of this country.

5. Membership issues. The following are significant: 1) our membership is aging, 2) we are losing members in the 30–39 age range, and 3) district branches must be part of a dues structure formula.

6. Research alliance. This meeting is ample proof that Dr. Pardes' theme for the year has been established, activated, and accomplished. Dr. Pardes has presided over the decade of the brain, the birth of practice parameters, and outcomes research; we have seen significantly increased NIMH and ADAMHA budgets. We look forward to implementation of Dr. Benedek's new theme: "Our Children: Our Future."

Thank you for the privilege and honor of serving as your Secretary for the past year. APA staff have been marvelous; let me especially thank Carol Davis, JoAnn MacBeth, Lea Mesner, and Elise Zukerman for their unstinting, skillful, and loyal assistance. I look forward to working with you during the coming year. Every member of APA is welcome to attend any meeting of APA's components, except meetings of the Ethics Committee and Ethics Appeals Board or when a component goes into executive session. Your strong support is deeply appreciated; your recommendations for consideration by the Board or other components are most welcome.

SUMMARY OF ACTIONS

The actions of the Board of Trustees are grouped by topic, and the topics are arranged alphabetically. The date of each action is given in parentheses at the end of the action.

ABPN

1. Approved sending to the ABPN the following slate, in preferential order, of candidates for psychiatry director on the ABPN: Leah J. Dickstein, M.D., Peter E. Tanguay, M.D., Kenneth Z. Altshuler, M.D., William T. McKinney, M.D., and Jerry M. Wiener, M.D. (Sept. 1989).

2. Endorsed the recommendation of the ABPN that its policy be changed to allow residents in postgraduate year 4 to take part 1 of the certifying examination and recommended the following: a) that the examination be administered as late in the academic year as possible, b) that this policy be adopted as a trial for 5 years, and c) that the ABPN conduct a study at selected sites on the impact of this change (Dec. 1989).

3. Authorized APA to write to the ABPN to express its concern about the absence of minority representation among ABPN directors and invite the senior psychiatrist and the executive vice-president of the ABPN, Dr. Stephen Scheiber, to meet with the APA Board of Trustees in March 1990 to discuss this issue; further, authorized Dr. Sabshin to express to Dr. Scheiber APA's concerns and suggest that Dr. Scheiber meet with Dr. Melvin Sabshin, APA Medical Director, and Dr. Layton McCurdy, an ABPN director for psychiatry, to confer before the March Board meeting (Dec. 1989).

4. Requested the ABPN to work with APA in developing models for a voluntary recertification program consistent with the APA position statement on recertification (June 1989).

Advocacy

1. Authorized continuing the advocacy projects in the New Mexico and Washington, D.C., district branches with an additional $10,000 and $5,000, respectively, and authorized continuing the project in the Georgia district branch, with no new funding at this time; further, renewed the Ad Hoc Committee for the Pilot Advocacy Project for another year, requesting that it determine the outcome of the three pilot advocacy projects and provide specific criteria and an evaluation of the program to the Board before any expansion of the project (June 1989).

2. Endorsed a policy stating that APA should vigorously support mental health consumer, family, and citizen groups and referred the statement to the Joint Reference Committee and the APA Auxiliary for study and a report (Dec. 1989).

Aging

1. Approved submission of the names of Drs. Lawrence Lazarus, Peter Rabins, Gabe Maletta, Andrew Leuchter, and Benjamin Liptzin to the ABPN for consideration for appointment to a committee on geropsychiatry (June 1989).

2. Authorized the Council on Aging and the Task Force on Models of Practice in Geropsychiatry to seek outside funding (approximately $3,500), following established procedures and working in conjunction with the Medical Director's office, to supplement the task force's current budget for developing information on models (March 1990).

AIDS

1. Authorized APA staff to explore with the AMA the possibility of removing APA's name from the film "HIV Blood Test Counseling" (Sept. 1989).

2. Approved APA's cosponsorship, at no cost to APA, of the second annual AMA HIV conference, focusing on counseling, testing, and early care and held on June 19, 1990, in San Francisco (March 1990).

3. Authorized the APA to contact the ABPN, the National Board of Medical Examiners, the Accreditation Council for Graduate Med-

ical Education, and the Residency Review Committee for Psychiatry and request that they consider increasing HIV content in their psychiatry and behavioral sciences curricula and examinations (Sept. 1989).

4. Approved the "Position Statement Opposing Mandatory Name Reporting of HIV-Seropositive Individuals" (5), subject to the Assembly's approval (Sept. 1989).

5. Authorized the Commission on AIDS to seek outside funding to produce and distribute the "AIDS Primer," at no cost, to all residents in psychiatry, psychiatric residency training directors, and department chairpersons, following established procedures and working in conjunction with the Medical Director's office (Sept. 1989).

AMA

1. Ratified the Executive Action taken by the President, Speaker, and Medical Director to approve cosponsorship of the AMA National Conference on the Prevention of Family Violence and Victimization, Oct. 5–7, 1989, in Chicago, at no cost to APA (May 1989).

2. Endorsed resolution 12 of the AMA House of Delegates, adopted in June 1989, which calls on AMA to urge a) the Liaison Committee on Medical Education to amend the standards for accreditation of medical education programs leading to the medical degree, specifically, the part 2 standards regarding medical student admissions, to read, "In addition, there must be no discrimination on the basis of sex, age, race, creed, national origin, or sexual orientation" and b) the Accreditation Council for Graduate Medical Education to amend the general essentials of accredited residencies regarding eligibility and selection of residents to read, "There must be no discrimination on the basis of sex, age, race, creed, national origin, or sexual orientation" (Dec. 1989).

3. Approved APA's continued participation in the AMA/Specialty Society Practice Parameters Partnership and Forum and endorsed the mission statement (Dec. 1989).

American Journal of Psychiatry

1. Approved the appointment of Drs. Paul S. Appelbaum, Gary Jay Tucker, and George E. Vaillant to 4-year terms as Associate Editors of the *American Journal of Psychiatry*; their terms begin at the end of the 1990 APA annual meeting (March 1990).

American Psychiatric Press, Inc.

1. Reappointed Drs. Robert O. Pasnau and John A. Talbott each to a second 4-year term on the board of directors of the American Psychiatric Press, Inc. (May 1989).

Annual Meeting

1. Authorized bringing in house the writing, editorial management, and production of the *Daily Bulletin*, noting that responsibility will rest with the Scientific Program Committee, working in conjunction with the Division of Public Affairs, but there will be no additional cost to APA (June 1989).

2. Authorized the Council on Medical Education and Career Development and its components to seek outside funding, following established procedures and working in conjunction with the Medical Director's office, to support the following projects: a) a resource booth in the APA membership center at APA annual meetings for residents and medical students ($8,000 in the initial year and approximately $5,000 in subsequent years), b) a medical student day at annual meetings with activities, a luncheon, and an exhibit ("Careers in Psychiatry") that could be placed in the resource booth ($8,000 in the initial year and approximately $6,000 in subsequent years) (June 1989).

3. Directed the Council on Internal Organization to assume responsibility (or to designate a subcomponent within the council) for implementing the antidiscrimination policy approved by the Board of Trustees in December 1988—organizations that discriminate in recruitment or employment on the basis of gender, race, religion, or sexual orientation will be prohibited from recruiting or offering em-

ployment in APA exhibit areas—with the understanding that this policy would be in effect for the 1990 APA annual meeting; further, voted "that the designated component will receive any allegations of such discrimination and, in consultation with Legal Counsel, shall determine whether the allegation is substantiated and that, if any employer fails to cooperate with the component's effort to ascertain whether it discriminates, that failure shall be a sufficient basis for denying such employer the opportunity to recruit or offer employment in APA exhibit areas"; also, voted that the recommendation of the designated component should come to the Board of Trustees for final action (June 1989).

4. Approved the following policy statements with respect to recruitment efforts in APA exhibit areas: "(1) Any organization that wishes to conduct recruitment efforts in APA exhibit areas must agree that its policy is not to discriminate in recruitment or employment on the basis of gender, race, religion, sexual orientation, or physical/mental disability (execution of a contract with the APA for such exhibit space represents that the exhibitor agrees to this policy); and (2) any complaint by an APA member, alleging that the organization has an established policy of discriminating on the basis of gender, race, religion, sexual orientation, or physical/mental disability, will be investigated by the APA which, based on its findings, reserves the right not to contract for future exhibitor space with the exhibitor" (Sept. 1989).

5. Approved the revised violations policy, to be included in the 1990 APA exhibitor prospectus, presented by the Council on Internal Organization (Sept. 1989).

6. Approved including $10,000 in the 1990 annual meeting budget to fund a limited trial of sign-language interpreters for hearing-impaired APA members (Sept. 1989).

7. Authorized the Assembly Committee of Representatives of Minority/Underrepresented Groups to seek outside funding (up to $6,000), following established procedures and working in conjunction with the Medical Director's office, to support a reception during the APA annual meeting in New Orleans in 1991 (March 1990).

8. Authorized the Assembly Committee of Representatives of Minority/Underrepresented Groups to seek approximately $40,000 from outside sources for a reception at the United Nations during the 1990 APA annual meeting in New York City (June 1989).

9. Authorized the Assembly Committee of Representatives of Minority/Underrepresented Groups to seek outside funding (up to $6,000) to support a symposium at the 1990 annual meeting, following established procedures and working in conjunction with the Medical Director's office (Sept. 1989).

10. Authorized the Committee of American Indian/Alaskan Native Psychiatrists to seek outside funding, following established procedures and working in conjunction with the Medical Director's office, to support a component workshop at the 1990 APA annual meeting (travel expenses for invited speakers) (June 1989).

11. Authorized the Task Force on Psychological Aspects of Nuclear Issues to seek outside funding, following established procedures and working in conjunction with the Medical Director's office, to support continued interviews with experts on nuclear arms control issues (June 1989).

12. Authorized the Committee on Occupational Psychiatry to seek outside funding, following established procedures and working in conjunction with the Medical Director's office, to support a reception at the 1990 APA annual meeting for psychiatrists interested in occupational psychiatry (June 1989).

13. Authorized the Committee on Private Practice to seek outside funding ($4,000–$6,000, depending on the size of the event) to support an invitational forum for private practitioners at the 1990 annual meeting, following established procedures and working in conjunction with the Medical Director's office (Dec. 1989).

14. Approved Philadelphia as the site for the 1994 APA annual meeting, to be held on May 21–26, 1994, and voted to authorize the Office of Meetings and Exhibits Management, in conjunction with legal counsel, to enter into the contracts necessary to secure the commitment with appropriate legal recourse in the event of labor strikes or other disruptions that could delay construction of the necessary facilities (March 1990).

15. Authorized the Committee on Women to seek $8,000 from

outside sources to continue its activity center at the 1990 APA annual meeting (June 1989).

Awards

1. Expanded the eligibility criteria for the Blanche F. Ittleson Award for Research in Child Psychiatry to allow consideration of psychiatrists whether or not they are Board certified or "Board eligible" as child psychiatrists, as long as their major research area has been child psychiatry; further, approved limiting candidates for this award to psychiatrists with works published in the past 5 years (June 1989).

2. Established the four-member Distinguished Service Awards Committee, which will collect and consider recommendations for nominees for (both individual and institutional) Distinguished Service Awards and recommend recipients to the Board of Trustees, with the understanding that the President-Elect will designate, with the concurrence of the President, the committee membership during his or her term in that office and that the committee may include members of the Board of Trustees and representatives of various components; and further, recommended that the new Distinguished Service Awards Committee during its first meeting review and consider refinement of the recommendations of the Long Range Planning Committee (June 1989).

3. Approved the following recipients for the 1990 Distinguished Service Awards: Gerald L. Klerman, M.D., Daniel X. Freedman, M.D., and the National Alliance for Research on Schizophrenia and Depression (Sept. 1989).

4. Approved the procedures and criteria for the Distinguished Service Award (Sept. 1989).

5. Authorized the Foundations' Fund Prize Board for Research in Psychiatry to seek outside funding to increase the honorarium to $10,000, following established procedures and working in conjunction with the Medical Director's office (Dec. 1989).

6. Established the Public Affairs Network Award (Dec. 1989).

7. Approved revisions to several aspects of the District Branch Newsletter of the Year Award (Dec. 1989).

8. Approved the principle that an award which is usually presented to an individual may occasionally be presented to a group, when deemed appropriate by the relevant award board or component (June 1989).

9. Asked staff to review the award process in general to identify problems and suggest changes and asked that this item be placed on the agenda of the Board's June 1990 meeting (March 1990).

10. Approved revisions to the conditions for the Robert T. Morse Writers Award and the Robert L. Robinson Award (Dec. 1989).

11. Established the Nancy C.A. Roeske Certificate of Recognition for Excellence in Medical Student Education (June 1989).

12. Approved publication, by Mead Johnson Pharmaceutical Division, of a brochure on the Solomon Carter Fuller Award (Dec. 1989).

13. Established the Wisniewski Young Psychiatrist Award, with the proviso that the Wisniewski family and the Institute for Basic Research continue to raise funds for the award until a principal of $25,000 has been accumulated (Dec. 1989).

Children and Adolescents

1. Ratified the Executive Action taken by the Senior Vice-President, Speaker, and Acting Medical Director to approve APA cosponsorship of the Child Mental Health Conference held on June 8, 1989, in Washington, D.C. (June 1989).

2. Authorized the Committee on Family Violence and Sexual Abuse and the Council on Children, Adolescents, and Their Families to seek outside funding (approximately $8,000) in support of secretarial and editorial assistance with their book, *Family Violence: A Clinical Guide*, following established procedures and working in conjunction with the Medical Director's office (Dec. 1989).

3. Ratified the Executive Action taken by the President, Speaker, and Medical Director to approve the "Statement on Psychiatric Hospitalization of Adolescents" (June 1989).

4. Voted to rescind the 1969 position statement on the use of drugs in schools (Dec. 1989).

Commendations

1. Approved sending a letter from APA to express appreciation to the Minnesota American Legion and American Legion Auxiliary for their efforts to aid persons suffering from chronic mental illness and related diseases and their endowment of a brain research professorship (University of Minnesota) at the Minneapolis Veterans Affairs Medical Center (June 1989).

2. Authorized sending a letter of commendation and appreciation to C. Everett Koop, M.D., for his outstanding efforts on behalf of the health and mental health of the American people during his tenure as Surgeon General (June 1989).

Components

1. Established the following components: Council on Addiction Psychiatry (June 1989); Board of Trustees—Ad Hoc Committee on the Annual Business Meeting and Forum (Dec. 1989), Ad Hoc Committee on Managed Care Issues (Dec. 1989), Distinguished Service Awards Committee (June 1989) (revised charge, Sept. 1989); joint Board and Assembly—Joint Board and Assembly Work Group on Practice Parameters (March 1990), Joint Board and Assembly Ad Hoc Committee on Membership and Fiscal Policies (Dec. 1989); Council on Aging—Committee on Long Term Care and Treatment for the Elderly (Dec. 1989), Task Force on Models of Practice in Geropsychiatry (June 1989); Council on Children, Adolescents, and Their Families—Task Force on Day Care for Preschool Children (Dec. 1989); Council on Economic Affairs—Committee on Quality Assurance (new component members and new charge) (March 1990), Committee on Managed Care (June 1989) (revised charge, March 1990); Council on International Affairs—Committee on International Education (Dec. 1989); Council on National Affairs—Corresponding Task Force on Psychiatric Dimensions of Disaster (Dec. 1989); Council on Psychiatric Services—Task Force on Family Systems and Family Therapy (Dec. 1989), Task Force on the Homeless Mentally Ill (June 1989), Committee on Psychiatric Services in Jails and Prisons (June 1989); Council on Research—Task Force on Neuropsychiatric Aspects of Traumatic Brain Injury (Dec. 1989), Committee on Research Training (June 1989).

2. Renewed the following components: Ad Hoc Committee to Develop a Slate of Candidates for Election to the American Board of Psychiatry and Neurology, Ad Hoc Committee to Evaluate Quality Assurance Activities, Ad Hoc Committee on Hospitalization of Adolescents, Ad Hoc Committee on Liaison Activities, Ad Hoc Committee on Legislation Affecting Quality of Care, Ad Hoc Committee for the Pilot Advocacy Project, Ad Hoc Committee to Revise Procedures for Nominating the Member-in-Training Trustee-Elect, Ad Hoc Committee on Subspecialization (June 1989).

3. Made the following changes to existing components: revised the charge to the APA Ethics Committee (March 1990); authorized the Resource Development Committee, which reports to the Budget Committee, to have liaison with the Board of Trustees and the district branches (Dec. 1989); authorized appointing the chairperson of the Committee to Coordinate the Functions of the H&CP Service, *Journal*, and Institute to the *H&CP* editorial board as an ex officio member (Dec. 1989); established duties for Assembly liaisons to APA components (June 1989); Board of Trustees—changed the Work Group on Codes and Reimbursements from a component of the Board of Trustees to a component within the Council on Economic Affairs, with the understanding that it would make timely reports to the Board and other components as needed (March 1990), revised the charge of the Executive Compensation Advisory Committee (March 1990), adopted changes in the tenure, composition, and charge of the Long Range Planning Committee (Sept. 1989); Council on Economic Affairs—transferred the Committee on Occupational Psychiatry from the Council on National Affairs to the Council on Economic Affairs (Dec. 1989); Council on Medical Education and Career Development—revised the charge of the Committee on Continuing Education to incorporate the remaining functions of the Committee on Independent Study, which was discharged (Dec. 1989), changed the name of the Committee of Residents to the Committee of Residents and Fellows so that the name more accurately reflects the composition of the committee (Dec. 1989); Coun-

cil on National Affairs—transferred the Committee on Occupational Psychiatry from the Council on National Affairs to the Council on Economic Affairs (Dec. 1989); Council on Psychiatric Services—changed the name of the Committee on State Mental Health Systems to the Committee on State and Community Psychiatry Systems and adopted a revised charge (Dec. 1989), created a 3-year position of Special Consultant for the Psychiatric Placement Service on the H&CP Service Committee (Dec. 1989), established a consultant position on the Committee on Psychiatric Services in the Military to permit representation of the Public Health Service (June 1989), changed the name of the Committee on Veterans Administration Affairs to the Committee on Veterans Affairs (June 1989); Council on Research—revised the charge to the Council on Research to include responsibility for development, oversight, and implementation of procedures for dealing with and reporting possible misconduct in science, in accordance with the rules established under the Public Health Service Act (Dec. 1989), changed the name of the Task Force on Educational Activities for DSM-III-R to the Task Force on Educational Activities for Diagnostic Systems (June 1989), revised the charge to the Committee on Biographical Directory and Related Research and changed its name to the Committee on the Biographical Directory and Research on Psychiatric Professional Activities (June 1989).

4. Discharged the following components: Board of Trustees—Ad Hoc Committee to Evaluate Quality Assurance Activities and the informal committee chaired by Dr. Robert Gibson that advised the Medical Director during the termination of the APA quality assurance program (March 1990), Ad Hoc Committee to Study the Composition of the Board (Sept. 1989), Ad Hoc Committee on Conflicts of Interest (June 1989), Ad Hoc Committee on Guidelines for Executive Sessions of the Board (June 1989), Ad Hoc Committee to Study Officers' Meetings and Other Board Retreats (June 1989); Council on Economic Affairs—Committee on Quality Assurance (March 1990, to be effective at the close of the annual meeting in May 1990); Council on International Affairs—Task Force on International Education (Dec. 1989); Council on Psychiatric Services—Committee on Psychiatrist Leadership in Public Mental Health (Dec. 1989), Task Force on Professional Practice Issues in Organized/Managed Care Settings (Dec. 1989), Task Force on Psychiatric Services in Jails and Prisons (June 1989); Council on Medical Education and Career Development—Committee on Independent Study (Dec. 1989); Council on Research—Task Force on Treatments of Psychiatric Disorders (Dec. 1989).

Economic Affairs

1. Voted to continue the Work Group on Codes and Reimbursements with the goal of developing a new, comprehensive coding system for psychiatry; and voted to refer this matter to the Joint Reference Committee and the Work Group on Codes and Reimbursements within the Council on Economic Affairs (Dec. 1989).

2. Authorized APA to issue a statement in support of efforts by the California Psychiatric Association to defeat the proposed $200 million cut in the California mental health budget and approved a statement for release to the news media (May 1989).

3. Approved "A Marketing Manual for the District Branches" for distribution to the district branches and Assembly (Dec. 1989).

Education

1. Authorized the Medical Director to convey a message to the Council of Medical Specialty Societies for transmission to the Accreditation Council for Graduate Medical Education saying that the council's general requirements were acceptable as revised (Sept. 1989).

2. Voted to end the Clearinghouse on Medical Student Electives and incorporate its contents into the "Directory of Psychiatric Residency Training Programs," beginning with the 1992 edition (Dec. 1989).

3. Authorized development of a survey to poll a representative sample of members who have not been certified by the ABPN to find out how APA can assist them in becoming certified (June 1989).

4. Authorized the Council on Medical Education and Career De-

velopment to seek outside funding (approximately $10,000), following established procedures and working in conjunction with the Medical Director's office, to pay for the reprinting of 10,000 copies of "Psychiatric Residents as Teachers," which is currently distributed to training programs (June 1989).

5. Approved the publication of the "Handbook for Directors of Psychiatric Residency Training Programs," with the appropriate disclaimer statements, as a joint project by APA and the American Association of Directors of Psychiatric Residency Training (March 1990).

6. Approved communicating to the Council of Medical Specialty Societies, for transmission to the Accreditation Council for Graduate Medical Education, the following wording on resident safety for inclusion in the council's general requirements: "Procedures for assuring resident safety which include, but are not limited to, providing a weapon-free and safe environment, and adequate training in the identification and management of the violent patient" (Sept. 1989).

7. Ratified the Executive Action taken by the President, Speaker, and Medical Director to authorize APA's submission of a request to the Pew Memorial Trusts for funding of the following activities related to collaboration between state mental health programs and academic departments of psychiatry: an ongoing staff office, consultation, information dissemination, networking, and an interorganizational consortium to determine priorities (May 1989).

8. Authorized sending a letter to the Residency Review Committee for Psychiatry encouraging it to consider accreditation of subspecialty fellowship programs (Dec. 1989).

Elections

1. Authorized staff to destroy the ballots from the 1989 election immediately after the 1989 annual meeting (May 1989).

2. Authorized the Elections Committee to continue to follow up on the small number of duplicate ballots mailed in the 1990 election and voted to use the Executive Action mechanism if any further action is necessary, with the understanding that all candidates for national office would be consulted and no decision would be taken without their consensus (March 1990).

3. Ratified an Executive Action taken by the President, Speaker, and Medical Director to authorize APA staff to conduct a survey of APA voting members with the zip code prefix 981 to determine how many duplicate ballots were mailed (March 1990).

4. Approved the following addition to section II.A.7. of the election guidelines: "Candidates will be asked to read APA's Policy on Conflict of Interest and Disclosure Statements and to sign the disclosure statement" (Sept. 1989).

5. Approved revised procedures for nominating the Member-in-Training Trustee-Elect to allow nominations to be made in the same way as for other trustee positions and to add the requirement that the Member-in-Training Trustee-Elect not serve in any other resident position (March 1990).

6. On the basis of the mail ballot, certified the results of the 1989 elections as reported by the Committee of Tellers (May 1989).

7. Endorsed in principle a survey of voters who may have received duplicate ballots, as proposed by the Elections Committee, but asked that the questions be designed in conjunction with the Office of Research and that the placement of the survey be carefully considered (Sept. 1989).

Ethics

1. Approved the following annotation to section 4 of "The Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry": "Sexual involvement between a faculty member or supervisor and a trainee or student, in those situations in which an abuse of power can occur, often takes advantage of inequalities in the working relationship and may be unethical because: a) any treatment of a patient being supervised may be deleteriously affected; b) it may damage the trust relationship between teacher and student; and c) teachers are important professional role models for their trainees and affect the trainees' future professional behavior" (June 1989).

2. Appropriated $50,000 in the 1990 APA budget to cover the cost of district branch ethics committees' consultation of Onek, Klein & Farr for guidance regarding the implementation of the revised "Procedures for Handling Complaints of Unethical Conduct" (Sept. 1989).

3. Extended the original indemnification of district branches against legal expenses and/or damages, not otherwise covered by insurance, incurred in suits based on actions related to ethics complaints to cover, under specified circumstances, individual members of the district branches and district branch staff for their ethics-related activities (March 1990).

4. Ratified an Executive Action taken by the President, Speaker, and Medical Director to indemnify individual members of the Maryland Psychiatric Society and its ethics committee who have been sued by an APA member because of an ethics case, extending the coverage provided by their own liability insurance or APA's liability insurance (March 1990).

5. Approved the request of the APA Ethics Committee that it be authorized to hold a workshop for chairpersons of district branch ethics committees and authorized spending $21,486 from the Board contingency fund for the workshop (June 1989).

6. Approved a revised description of the APA Ethics Committee for publication in the next update of the "Operations Manual of the Board of Trustees" (March 1990).

7. Approved the revised "Procedures for Handling Complaints of Unethical Conduct," which took effect on Oct. 14, 1989, with the understanding that a companion document would be developed (June 1989).

Fiscal Issues

1. Approved a 10% increase for all member dues categories for the 1990 fiscal year; approved in principle the remainder of the budget as recommended by the Budget Committee and postponed final approval until December 1989, after fine tuning of the budget; and approved merit pay increases for staff averaging 5.5% and an increase for inflation of 5.2% for nonsalary budget items (Sept. 1989).

2. Approved an across-the-board 1% reduction from 1989 levels for component and department budgets and major reductions in travel expenses for all departments; approved a 1990 APA budget of $23,959,231 (Dec. 1989 and March 1990).

3. Approved the establishment of an APA checking account at the Manufacturers Hanover Trust of New York for cash and checking operations at the 1990 annual meeting (March 1990).

4. Approved a resolution enabling APA to maintain and use an account at Bear, Stearns, and Company, Inc. (Dec. 1989).

5. Approved the corporate resolution relative to the execution of any and all documents required to reestablish APA's line of credit with the National Bank of Washington, which provides a maximum borrowing level of $4 million (June 1989).

6. Allocated $5,250 from the Board contingency fund, with the understanding that the Joint Reference Committee would contribute an equal amount from its new component fund, to support the following newly established components for the remainder of 1989: Ad Hoc Committee on Managed Care ($4,000), Task Force on the Homeless Mentally Ill ($2,500), and the Committee on Research Training ($4,000) (June 1989).

7. Allocated $13,000 for a feasibility study regarding the costs and benefits of psychotherapy (Dec. 1989).

8. Allocated $7,500 from the 1990 Board of Trustees contingency fund to support three new components: Task Force on Day Care for Preschool Children ($2,500), Task Force on Family Systems and Family Therapy ($3,000), and Task Force on Neuropsychiatric Aspects of Traumatic Brain Injury ($2,000) (Dec. 1989).

9. Allocated $10,000 from the 1989 Board contingency fund for APA membership in the National Council of State Legislatures and in the American Legislative Exchange Council; voted to allocate $5,000 from the 1990 Board contingency fund for APA membership in the Council of State Governments (Dec. 1989).

10. Clarified that, as passed by the Board in December 1988, the one-time dues amnesty applies only to members who rejoin during 1990 and who owe dues for years before 1988 (Dec. 1989).

11. Approved interim guidelines for resource development as presented to the Board in March 1989 and as amended by the Resource Development Committee (June 1989).

12. Approved in principle the strategic plan for organization of the Office of Resource Development (Dec. 1989).

13. Approved the following mission statement for use in fund-raising activities: "The APA is committed to the need for a broad-based fundraising initiative among members, corporations, foundations and the lay public. These funds will advance the prevention, diagnosis and treatment of mental illness. They will support projects in research and public education, innovative service programs and other special purposes" (Dec. 1989).

14. Approved the name "Fund for the Future—APA" as the umbrella designation for APA's fund-raising programs (Dec. 1989).

15. Approved the implementation of the Tribute Fund, which will provide a convenient method of giving gifts or commemorations (Dec. 1989).

16. Authorized in principle the development of specific plans for an annual giving program and a comprehensive planned giving program, details of which will be presented at a future Board of Trustees meeting (Dec. 1989).

17. Authorized the Resource Development Committee to approach Life Members and Life Fellows for contributions to inaugurate the Fund for the Future—APA (Dec. 1989).

18. Adopted the APA pension plan as presented to the Board during the June 1989 meeting and authorized the Medical Director to take such actions as are necessary to implement this resolution (June 1989).

19. Approved the following resolution relative to contracts for the guaranteed long-term account of the 401(k) plan: "(1) that the Guaranteed Long Term Account of the American Psychiatric Association Retirement Savings Plan continue to be invested in guaranteed investment contracts (GICs) or similar contracts issued by life insurance companies; (2) that all such contracts should be issued by life insurance companies with assets exceeding one billion dollars which have a Best's Rating of A+; (3) that the Association instruct its benefits consultant, Grubbs & Company, to seek and analyze proposals for such contracts, taking into account the length of the guarantee period, the guaranteed rates of return, contract provisions, and other relevant considerations; and (4) that the Medical Director or his delegate be authorized to direct the Trustee of the Plan to enter such contracts as he deems appropriate for funding the Plan, subject to approval by Legal Counsel" (Dec. 1989).

20. Approved the following resolution relative to implementation of the APA pension plan: "(1) that the proposed American Psychiatric Association Pension Plan be adopted; (2) that the Association enter the proposed Trust Agreement with Sovran Bank, N.A., as Trustee of the above plan; and (3) that the Medical Director or his delegate be authorized to take such steps as are necessary to implement the above, including adopting any amendments to the Plan documents required by the Internal Revenue Service for approval of the plan" (Dec. 1989).

Get Well Wishes

1. Voted to send best wishes and flowers from the Board of Trustees to Dr. Robert Campbell during his convalescence from surgery (Dec. 1989).

2. Voted to send best wishes from the Board to Dr. William Webb during his convalescence and treatment at the Mayo Clinic (Dec. 1989).

3. Authorized Dr. Sabshin to send a communication on behalf of the Board of Trustees to Dr. Pete Wellborn, expressing the best wishes of the members of the Board during his illness (Sept. 1989).

Governance

1. Approved an amendment to chapter 1.12 of the Bylaws for reading at the 1990 annual meeting and for placement on the 1991 ballot; this amendment would extend the option of Corresponding Membership to psychiatrists living in Mexico, Central America, and the Caribbean (Dec. 1989).

2. Approved amendments to chapter 1.4(a), chapter 2.1 and 2.2,

and chapter 8.6 of the Bylaws for reading to the membership at the 1990 annual meeting and for placement on the 1991 ballot; these amendments would exempt medical students from the dual membership requirement and from yearly dues, so they would pay only a one-time fee when they join (Dec. 1989).

3. Approved amendments to chapter 1 paragraphs 4(b) and 5 of the Bylaws for reading to the membership at the 1990 annual meeting and for placement on the 1991 ballot; these amendments would abolish the category of Associate Membership (March 1990).

4. Requested that the Committee on Constitution and Bylaws continue to actively examine the Constitution and Bylaws, bringing them into conformity with current practice whenever necessary (Dec. 1989).

5. Approved the "Statement of the Mission, Goals and Objectives of the American Psychiatric Association" as revised (Sept. 1989).

6. Endorsed a set of duties for Assembly liaisons (June 1989).

7. Established a Board liaison position on the Resource Development Committee, with the understanding that it would be a voting position and that the decision to appoint such a liaison would be at the discretion of the President (Dec. 1989).

8. Approved the report of the Ad Hoc Committee on Conflicts of Interest and requested the Medical Director to implement the recommendations concerning its distribution and requirements for signing disclosure statements by APA officials, members of and consultants to APA components, and APA staff; further, discharged the Ad Hoc Committee on Conflicts of Interest with an expression of appreciation (June 1989).

9. Supported the concept of integration of special psychiatric professional identities into APA and referred back to the Long Range Planning Committee a number of governance issues, requesting the committee to develop options for the Board's consideration (June 1989).

10. Approved a waiver of current policy to permit Dr. Donald Fidler to serve an additional year (through May 1991) as chairperson of the Subcommittee on Video (Dec. 1989).

11. Approved a waiver of current policy to permit Dr. Harvey Bluestone to serve an additional year (through May 1991) as chairperson of the Committee on Member Life, Accident and Health Insurance (March 1990).

12. Voted to implement, insofar as possible, the intent of the Area VI action paper which proposes that APA continue to be concerned about the environmental impact of the day-to-day operations of the APA Central Office and that it find ways to recycle paper used at meetings and develop other mechanisms to conserve paper (Dec. 1989).

Homeless Mentally Ill

1. Authorized the Task Force on the Homeless Mentally Ill to pursue liaison with the American Bar Association's homelessness project, at no cost to APA (March 1990).

2. Accepted the statement "General Directions for Public Policy in Behalf of the Mentally Ill Among the Homeless Population" as an interim task force report for appropriate use by APA to further psychiatry's involvement in relevant federal, state, and community activities, with the understanding that the statement will be reviewed by the Council on Psychiatric Services and the Joint Reference Committee and, if changes are made, will be returned to the Board for subsequent approval (March 1990).

Hospital and Community Psychiatry

1. Approved appointment of the following to the *H&CP* editorial board for one 4-year term each: Drs. Steven M. Mirin and Jose M. Santiago (May 1989), Dr. James H. Shore (Dec. 1989), and Drs. Carl Bell, Mary Jane England, and Miles F. Shore (March 1990); approved Dr. Robert O. Friedel's reappointment to a second 4-year term on the *H&CP* editorial board (Dec. 1989).

2. Authorized increased fees for the 1990 H&CP Institute (Dec. 1989).

Insurance Programs

1. Approved in principle adding a medical defense plan to APA's professional liability insurance program; obtaining, if possible, a second bid; and, if feasible, offering the plan to members insured through their institutions (Dec. 1989).

2. Authorized offering the MEDEFENSE policy from Calvert Insurance to members holding APA professional liability insurance and those who receive coverage through their institutions and do not purchase liability coverage on the general market (March 1990).

3. Authorized a 40% increase in the premiums of the APA major medical health insurance program, effective Aug. 1, 1989, with the understanding that within the next few months members would be offered the new health insurance program that was authorized by the Board in March 1989 (June 1989).

4. Ratified the Executive Action taken by the President, Speaker, and Medical Director a) to authorize Treasurer Dr. Alan Levenson, on behalf of the American Psychiatric Association Insurance Trust, to execute a nonnegotiable demand note in the amount of $4,000,000 in favor of the American Psychiatric Association Risk Retention Group and b) to authorize the execution of a related indemnification and assumption agreement, pursuant to which Psychiatrists' Mutual Insurance Company, Inc., assumed all obligations of the trust under the note in question and by which Psychiatrists' Mutual fully indemnified the trust and held it harmless for all actions taken in connection with the note (May 1989).

5. Approved requiring that all members of the Board Committee on Insurance, the board of Psychiatrists' Mutual Insurance Company, and the Risk Management Committee on the APA Insurance Trust sign agreements of confidentiality and noncompetition and agree not to testify in malpractice suits involving insured APA members, with the understanding that such agreements are to be reviewed and approved by legal counsel (March 1990).

6. Authorized offering to holders of APA-sponsored professional liability insurance (except those in New York State, because of state requirements) an excess coverage of $1 million per incident over the $1 million per incident coverage (which is now the highest level sold) through Union America (a subsidiary of Continental Insurance) (March 1990).

7. In executive session, upheld the decision of Professional Risk Management Services, Inc. (PRMS) to deny a member's request for reimbursement for expenses that are not covered under the insurance agreement (Sept. 1989).

8. Authorized the Medical Director and legal counsel to enter into good faith negotiations with the Galtney Group, Inc., for the disposition of APA's common preferred stock interests in PRMS at the price presented in the Galtney Group letter of Nov. 28, 1989, with the understanding that the final decision regarding price and other terms of the transaction are to be made by Executive Action before the closing; further, instructed the Medical Director and legal counsel to assure that APA receive certain rights and assurances in the agreements related to the sale (Dec. 1989).

9. Ratified the Executive Action to complete the sale of APA's interest in PRMS; ratified the actions taken by Dr. Levenson as director of PRMS in consummating the sale; approved Dr. Levenson's appointment as an APA representative to PRMS, now that it is a subsidiary of the Galtney Group, and as a nonvoting (advisory) director of PRMS after the sale; and indemnified Dr. Levenson for his actions as a voting and nonvoting member of the board of PRMS (March 1990).

International Affairs

1. Approved cosponsorship with the Pacific Rim College of Psychiatrists of the Second International Symposium on Psychiatric Research in Asia, to be held in Hawaii in February 1992, and authorized the Committee of Asian-American Psychiatrists to seek outside funding (approximately $25,000) to support the symposium, following established procedures and working in conjunction with the Medical Director's office (Dec. 1989).

2. Waived the restriction on the timing of international meetings and approved APA's exploration of the possibility of having a joint meeting with the Caribbean Psychiatric Association and/or the Cen-

tral America and Panama Psychiatric Society immediately after the annual meeting in New Orleans in 1991 (Dec. 1989).

3. Approved the dates Sept. 30–Oct. 1, 1990, for a joint meeting with the German Society of Psychiatry and Nervous Diseases in Bonn (June 1989).

4. Extended the apology of the APA Board of Trustees and the apology expressed by the German Society of Psychiatry and Nervous Diseases to all people who have experienced hurt from the scheduling of the joint meeting between APA and the German society during Yom Kippur; revised the meeting schedule so that no part of the program or the need for travel occurs during Yom Kippur (the joint meeting will begin on Oct. 1, 1990, and the satellite symposia in Mainz will be followed by satellite symposia in Mannheim/Heidelberg on Oct. 24 and an Oct. 4–5 session in Munich; the plenary sessions will be held on Oct. 6–7, 1990, in Bad Kissingen) (March 1990).

5. Authorized the Council on International Affairs and its Task Force on International Education to seek funding from the International Medical Students Program to support part-time positions for work by APA connected with that program; approved, in principle, the hiring of a psychiatrist, one-fifth time, and an APA staff person, one-half time, to administer the consultancy to the International Medical Students Program (June 1989).

6. Authorized APA's submission of the new Operational Instrument for the WPA Review Committee as a formal resolution for vote in October 1989 by the WPA General Assembly; further, authorized APA's delegate to attempt to bring this resolution before the General Assembly before any discussion or vote on the readmission of the All Union Society of Psychiatrists and Narcologists of the USSR and voted to empower APA's delegate and leadership to negotiate as events proceed (June 1989).

7. Allocated $3,000 from the Board contingency fund to pay the registration fee and partial expenses of the APA delegate to the WPA General Assembly meeting in Athens during October 1989 (June 1989).

8. Voted to view with favor the positions of the Royal College of Psychiatrists and the German Society of Psychiatry and Nervous Diseases with respect to the admittance into the WPA of the All Union Society of Psychiatrists and Narcologists of the USSR and asserted that APA would retain the flexibility to submit an independent resolution, such as recommending continuation of ad hoc membership to the All Union Society; further, authorized use of the Executive Action mechanism in a final decision before the deadline for submission of resolutions to the WPA (early September 1989) (June 1989).

9. Endorsed the following principle concerning changes in the WPA voting structure: "The APA will seek a voting structure that respects larger societies for their significant membership but that protects smaller societies by giving them a vote that is disproportionate to the actual membership size" (June 1989).

10. Approved the recommended amendment to the WPA statutes and bylaws related to the Committee to Review Abuses of Psychiatry and voted to submit the resolution to the WPA for vote at the General Assembly meeting in October 1989 (Sept. 1989).

11. Approved amendments, as recommended by the Council on International Affairs, to the resolutions submitted by APA to the WPA regarding the admission into the WPA of the All Union Society of Psychiatrists and Narcologists of the USSR (Sept. 1989).

JCAHO

1. Endorsed the concept that APA write a letter to the JCAHO recommending that it require hospitals to have standards for admissions and that it examine these standards during the process of hospital accreditation; further, recommended that this concept be considered by the Assembly in May 1990 and that, if the Assembly agrees, the letter be sent (March 1990).

2. Endorsed a resolution asserting the importance of effective medical leadership for the proper management of hospital organizations and delineating specific actions, including encouraging the AMA Section Council on Psychiatry and the district branches to contact the JCAHO and its board of commissioners, to advocate

continuation of the requirement for medical staff organization in state hospitals (Dec. 1989).

3. Reaffirmed the principles by which standards for psychiatric facilities are developed, reaffirmed APA's commitment to state hospital systems, and endorsed APA's continued involvement in activities that support public sector practice (Sept. 1989).

Judicial Activities

1. Ratified the Executive Action taken by the President, Speaker, and Acting Medical Director to authorize APA to join other professional health care associations in filing a brief in *William L. Webster v. Reproductive Health Services* (May 1989).

2. Authorized APA to join the American College of Obstetricians and Gynecologists' amicus brief in the Supreme Court cases *Hodgson v. Minnesota* and *Akron Center for Reproductive Health v. Slaby*, which concern abortion rights for minors (Sept. 1989).

3. Authorized APA to join one of the amicus curiae briefs filed in the Supreme Court by the AMA and the American College of Obstetricians and Gynecologists in *Ragsdale v. Turnock*, which oppose the Illinois restrictions on locations in which abortions may be performed, with the understanding that the decision as to which brief best reflects APA's position would be made by the chairperson of the Commission on Judicial Action (Sept. 1989).

4. Approved payment of $5,000 to the American College of Obstetricians and Gynecologists for preparation of the briefs filed in the abortion cases before the U.S. Supreme Court (Dec. 1989).

5. Ratified the Executive Action taken by the President, Speaker, and Medical Director to authorize APA, along with the California Psychiatric Association and the Hawaii Psychiatric Society, to file a brief in the U.S. Supreme Court in the case *Doe v. United States*, which addresses confidentiality of a patient's psychiatric treatment records (Sept. 1989).

6. Approved payment of $1,000, on a matching basis, to the Indiana Psychiatric Society for preparation of the amicus brief filed by that district branch in the Indiana Court of Appeals in the case *In the Matter of C.P.* (Dec. 1989).

7. Authorized payment of $5,000, on a matching basis, to the Massachusetts Psychiatric Society for preparation of its amicus brief in *Rotman v. Mirin* (Dec. 1989).

8. Ratified an Executive Action taken by the President, Speaker, and Medical Director to authorize APA to file an amicus brief in *Walter Harper v. the State of Washington*, concerning a prisoner who refused treatment (May 1989).

9. Approved "Right to Refuse Medication" as a resource document for distribution to the district branches (Dec. 1989).

10. Ratified the Executive Action taken by the President, Speaker, and Medical Director to authorize APA, along with the AMA, to file an amicus curiae brief in the U.S. Court of Appeals for the Third Circuit in *Wilkerson v. Sullivan*, involving the disability criteria applied by the Social Security Administration to people suffering from alcoholism (Dec. 1989).

11. Ratified the Executive Action taken by the President, Speaker, and Medical Director to authorize APA to join a consortium of mental health organizations in filing an amicus brief in the U.S. Supreme Court for *Zebley v. Bowen*, a case challenging the restrictive disability standards for children currently being applied by the Social Security Administration (Sept. 1989).

12. Authorized APA to file an amicus brief in the U.S. Supreme Court in *Perry v. Louisiana*, a case addressing the issue of whether a mentally incompetent prisoner may be medicated with psychotropic drugs to restore him to competency so that he may be executed (March 1990).

Legislation

1. Voted to take the following position: "We are in favor of nondiscriminatory reimbursement in handling mental health benefits; we applaud anyone who makes an improvement in the mental health benefits; and we recognize that in the course of political developments the persons closest to the situation have to make strategic moves in response to each hurdle on the path to nondiscrimination" (March 1990).

2. Adopted the following resolution: "Cut-backs in funding and the trend of demedicalization in the public sector are against the interests of mental patients" (Dec. 1989).

3. Voted to indicate support, through the Joint Commission on Government Relations, for the principles outlined in the report of the President's Quadrennial Commission on Pay and voted to continue to lobby for the designation of psychiatry as a scarce specialty within the VA system (Dec. 1989).

Liaison Activities

1. Authorized the Ad Hoc Committee on Liaison Activities to continue to convene meetings of internal APA liaisons and representatives from related psychiatric organizations and authorized the committee to continue efforts to strengthen APA liaison with other organizations (June 1989).

2. Endorsed the concept of developing task forces, or finding creative alternative ways, to formalize APA's liaison with groups that relate to the Council on Children, Adolescents, and Their Families, the Council on Medical Education and Career Development, the Council on Psychiatric Services, and the Council on Research (Dec. 1989).

Logo

1. Voted to change the APA logo to include "M.D." after Benjamin Rush's name, in preparation for APA's sesquicentennial in 1994 (March 1990).

Managed Care

1. Approved the Managed Care and Utilization Review Information Line (an 800 number) within the Office of Economics for immediate response to members' needs, with the understanding that funding and staff are to be provided in the 1990 budget (March 1990).

2. Ratified the Executive Action taken by the President, Speaker, and Medical Director allowing the reallocation of funds to develop economic data on mental health and substance abuse services (March 1990).

3. Approved the "Guidelines for Psychiatric Practice in the Staff Model HMOs" (June 1989).

4. Approved revisions to the charge of the Committee on Managed Care to encourage its implementation by the September 1990 components meetings (March 1990).

5. Approved a public relations strategy for managed care, which would include the production of a "Managed Care Survival Manual" for members and a series of media-related activities, including preparation of news releases and a fact kit on economic issues for the media (March 1990).

Member Benefits

1. Voted to postpone signing a contract with Raymond James Financial, Inc., and Grande Financial Services, Inc., for financial services for APA members (authorized by the Board in December 1988); further, voted to place on the June 1989 agenda of the Board a discussion of the pilot project, requesting legal counsel to analyze the situation and present recommendations (May 1989).

2. Voted to postpone further discussion of the financial planning services pilot project until September 1989 and referred the issue of contracting for financial planning services for APA members back to the Committee on Special Benefits, indicating that the Board is disinclined to go forward with the current proposal or similar ones, unless persuaded otherwise (June 1989).

3. Authorized offering to APA members the retirement fund program offered through Grande Financial Services as described in the proposal given to the Board, subject to the approval of the necessary legal agreements by APA legal counsel (March 1990).

4. Ratified an Executive Action taken by the President, Speaker, and Medical Director to change vendors from First Service Member Travel to Vantage Travel for the existing APA member travel program (which was approved by the Board in March 1987) (March 1990).

Membership

1. Advanced 204 members from General Member to Fellow and three members from Life Member to Life Fellow; deferred advancement of 34 members from General Member to Fellow (Dec. 1989).

2. Approved three applications for General Member-at-Large and approved one application for advancement from Associate Member-at-Large to General Member-at-Large (Dec. 1989).

3. Approved 29 applications for Corresponding Member, approved three nominations for advancement from Corresponding Member to Corresponding Fellow, and approved the nominations of eight nonmembers for Corresponding Fellow (Dec. 1989).

4. Approved election of Dr. Felice Lieh-Mak to Corresponding Fellow (March 1990).

5. As recommended by the Committee on Membership, approved the waiver, reduction, or refund of APA dues or transfer to Inactive status for 265 members, denied Inactive status or waiver or refund of APA dues to 53 members, and authorized other special membership processing actions for four members (June and Dec. 1989).

6. Voted to expel Dr. James Petroske from APA and from the Oregon Psychiatric Association for violating section 2, annotation 1, of "The Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry"; also, voted to expel Dr. Jeffrey Moran from APA and the Orange County Psychiatric Society for violating sections 1, 2, and 3 of "The Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry" (June 1989).

7. Expelled Dr. Marvin Ziporyn from APA and from the Illinois Psychiatric Society for noncompliance with the terms of his suspension and for violation of section 1, annotation 1, of "The Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry (March 1990).

8. Approved abolishing the category of Associate Member, with the understanding that the 295 members currently holding this status be permitted to retain it but that no new applicants would be accepted for this category; further, referred this action to the Committee on Constitution and Bylaws for its recommendations on appropriate Constitutional changes (Dec. 1989).

9. Approved the following ethics-related guidelines for inclusion in the membership section of the "Operations Manual of the Board of Trustees": "(1) an ethics investigation will not affect a member's eligibility to transfer to Life status prior to resolution of the investigation; (2) if a member fails to pay APA membership dues while an ethics investigation is being conducted, the member's district branch may request that the dropping action be delayed pending resolution of the ethics investigation (a written request must be submitted by the district branch to the APA Office of Membership); and (3) if a district branch submits a Fellowship nomination to the APA Committee on Membership while there are ethical issues pending, the Committee will disregard any information concerning these matters, other than a formal request from the district branch to withdraw the nomination" (Dec. 1989).

10. Approved revising the operations manual to state that the situations of members who transfer to Inactive status will be reviewed every 5 years to determine if continuation in that category is appropriate (Dec. 1989).

11. Approved revising the operations manual to establish a time limit for dropping from APA membership Members-in-Training who fail to advance to General Member within 1 year (Dec. 1989).

12. Authorized dropping from APA membership as of Oct. 1, 1989, three members who were in arrears for 1987 dues (Sept. 1989).

13. Authorized dropping from APA membership 463 members whose dues were in arrears for 1988; further, authorized administrative reinstatement for those who returned to good standing in APA by Jan. 31, 1990, and who were also in good standing in their district branches (Dec. 1989).

14. Authorized dropping from APA membership as of March 1, 1990, two members who were in arrears for 1988 APA dues (March 1990).

15. Authorized dropping from APA membership 193 members

who had been dropped or resigned from their district branches; further, authorized administrative reinstatement of those who returned to good standing in their district branches and who were also in good standing in APA (June, Sept., and Dec. 1989 and March 1990).

National Issues

1. Authorized the Committee of American Indian/Alaskan Native Psychiatrists to seek outside funding, following established procedures and working in conjunction with the Medical Director's office, to support travel for continued monitoring, in conjunction with the Joint Commission on Government Relations, of the mental health services available to Native Americans (June 1989).

2. Authorized the Committee on Psychological Aspects of Nuclear Issues to seek outside funding, following established procedures and working in conjunction with the Medical Director's office, to support a symposium and reception at the 1990 APA annual meeting for those interested in the topic (June 1989).

3. Established the five-member, 3-year Corresponding Task Force on Psychiatric Dimensions of Disaster within the Council on National Affairs (Dec. 1989).

4. Voted that there should be a component within APA (either an existing or new component) charged with studying universal/national health insurance and that a small working group of Drs. Edward Hanin, John McGrath, and Herbert Sacks will study various models, including Dr. Sacks's proposals and the action papers coming to the May 1990 Assembly meeting on this issue; further, this small working group will bring recommendations to the June Board meeting, including realistic cost estimates and proposed staffing for the component (March 1990).

NIMH

1. Agreed to communicate to NIMH the Assembly's concern about possible discrimination in funding of consumer group applicants, to ask NIMH to monitor funding practices as much as possible to determine whether there is discrimination against psychiatry or other professional groups in such funding, and to discourage such discriminatory funding whenever and wherever it occurs (Dec. 1989).

2. Authorized APA's participation in the Mental Health Leadership Forum and endorsed the following goals of the forum: "(1) to establish mental illness as one of the Nation's central and pressing health care responsibilities; (2) to raise the national health care priority of the mental illnesses to a level commensurate with their wide prevalence and the suffering and disability they cause; and (3) to galvanize a major national research and service effort to largely conquer the mental illnesses by the year 2000" (Dec. 1989).

3. Approved APA's recommendation to NIMH that meaningful psychiatrist input be required in the central office of mental health authorities in each state and that this requirement be enforced through implementation of the public law (Dec. 1989).

Practice Parameters

1. Supported the concept of developing acceptable practice parameters for psychiatric care and authorized APA to work with other appropriate organizations (e.g., the AMA) in the development of practice parameters, with appropriate consultation with legal counsel; further, voted that the Assembly and the Board would periodically review the clinical practice parameters as they are developed, before final approval (Dec. 1989).

2. Endorsed a memorandum of agreement that would enable the AMA, through collaboration with the AMA/Specialty Society Practice Parameters Partnership and Forum, to engage the Academic Medical Center Consortium and Rand Corporation in an advisory capacity to facilitate development of practice parameters by the national medical specialty societies, with the understanding that the letter acknowledging the agreement will be approved by means of Executive Action (March 1990).

3. Established the Joint Board and Assembly Work Group on Practice Parameters to address issues and make recommendations

with respect to how the Association can develop practice parameters (March 1990).

Psychiatric Services

1. After appropriate consultation with legal counsel, endorsed the following recommended minimum essential services to be provided in community mental health programs when faced with severe budgetary constraints: 1) diagnosis, referral, and consultation to community care givers, 2) 24-hour crisis intervention, including protective inpatient care when necessary, 3) continuity of treatment in a continuum of residential and social/vocational alternatives for seriously mentally ill adults and seriously emotionally disturbed children, and 4) adequate medical/psychiatric services to ensure proper treatment of all mentally ill patients, especially those who suffer from serious mental illness (June 1989).

2. Authorized the Committee on Occupational Psychiatry to seek outside funding, following established procedures and working in conjunction with the Medical Director's office, to support the administrative costs of preparing a curriculum on occupational psychiatry and to enable continuation of special meetings between APA leaders and corporate representatives (June 1989).

3. Authorized the APA Office of Research to work with the Committee on the Practice of Psychotherapy to assess the feasibility of a pilot study on the comprehensive cost-benefits of psychotherapy (Dec. 1989).

4. Authorized APA to continue, through the Joint Commission on Government Relations, lobbying strongly against programs for prescription of medication by nonphysicians and voted to encourage the AMA and its political action committee to assist with this lobbying effort (Dec. 1989).

5. Authorized APA to inform appropriate individuals in the U.S. Department of Defense that, regarding psychiatric services in the military, the position of the APA leadership is "to ensure that medical differential diagnoses and treatment planning are required for appropriate patients and patient populations and that hospital admitting privileges and prescription-writing privileges are granted only to those who have appropriate medical education, orientation, training and experience" (June 1989).

6. Approved the "Guidelines Regarding Psychiatrists' Signatures" (6) as revised, and authorized dissemination and publication of the revised version of these guidelines (June 1989).

7. Authorized the Committee on State and Community Psychiatry Systems to seek outside funding of a public psychiatry newsletter, following established procedures and working in conjunction with the Medical Director's office (Dec. 1989).

8. Encouraged the U.S. Department of Veterans Affairs (VA) and Congress to actively improve recruitment and retention of psychiatrists within the VA (June 1989).

9. Endorsed a proposal that, in addition to its current fellowship program, the VA develop 50 new fellowship positions in geriatrics, with special emphasis on geriatric psychiatry (June 1989).

10. Voted to indicate support, through the Joint Commission on Government Relations, for the retention of professional (physician) administrators in the VA central office (Dec. 1989).

Public Affairs

1. Endorsed the resolution of the APA Auxiliary, as approved at the meeting of the Auxiliary's Executive Council and as amended by the Assembly, calling on the officials of APA "to establish programs designed to educate and enlighten the citizenry of our country regarding mental illness and the unique role of psychiatric physicians in the diagnosis and treatment of mental illness, and . . . to seek collaboration with the AMA on these matters" (June 1989).

2. Authorized APA to work with the Institute of the Pennsylvania Hospital to develop and cosponsor a 1-day symposium addressing stigma, patient care, and public policy as part of the institute's celebration of its 150th year of operation, beginning in January 1991 (Dec. 1989).

3. Authorized the Joint Commission on Public Affairs to enter into an agreement with Martin Publishing, Inc., permitting use of the APA logo on a patient newsletter subscribed to by psychiatrists, with

the understanding that APA has complete editorial control, that the Joint Commission on Public Affairs and Division of Public Affairs would serve as an editorial panel, that the newsletter would include only enough blank space for printing the psychiatrist's name, that the only cost to APA would be for labels for an initial mailing to introduce the service to members, and that the agreement could be terminated by either party with appropriate notice (March 1990).

4. Approved the position statement "Use of Stigma as a Political Tactic" (March 1990).

Quality Assurance

1. Reaffirmed the action taken by the Board in June 1989 to continue pursuit of the CHAMPUS contract and authorized use of the Executive Action mechanism to initiate procedures for termination of APA's commercial utilization review projects and to sell its assets if CHAMPUS awarded the contract to another bidder (Sept. 1989).

2. Discharged the Ad Hoc Committee to Evaluate Quality Assurance Activities and the informal committee chaired by Dr. Robert Gibson that advised the Medical Director during the termination of the APA quality assurance program, with an expression of appreciation to the members serving on these committees (March 1990).

3. Authorized establishment, in May 1990, of the Committee on Quality Assurance within the Council on Economic Affairs; it will have five to seven members, and its charge is to be refined by the Council on Economic Affairs in consultation with others so that the committee can incorporate overlapping aspects of the Association's efforts regarding managed care (March 1990).

4. Discharged the Committee on Quality Assurance, effective at the close of the annual meeting, with a strong expression of appreciation to its members, who served many years and devoted much time and attention to APA's programs (March 1990).

5. Ratified the Executive Action taken by the President, Speaker, and Medical Director to authorize the Medical Director to initiate termination of APA's commercial utilization review projects (Dec. 1989).

RBRVS

1. Allocated $15,000 in additional funds from the 1989 Board contingency fund to enable the Work Group on the Harvard Resource-Based Relative Value Scale Study to hire consultants to fully analyze the legislative proposals now before Congress (Sept. 1989).

2. Voted to state to the work group on the RBRVS study that the Board finds the issues with which the work group is dealing of considerable moment and, on decisions of consequence, the Board would like the work group to consult, when feasible, with the Board or its Executive Action group (i.e., the President, Speaker, and Medical Director) (Dec. 1989).

3. Ratified the Executive Action taken by the President, Speaker, and Medical Director to approve the letter of Feb. 27, 1990, sent from Dr. Donald Scherl, chairperson of the Work Group on the Harvard Resource-Based Relative Value Scale Study, to Dr. William Hsiao, principal investigator of the Physician Payment Relative Value Study (March 1990).

Religion and Psychiatry

1. Approved and authorized publication of "Guidelines Regarding Possible Conflict Between Psychiatrists' Religious Commitments and Psychiatric Practice" (7) (Dec. 1989).

Research

1. Authorized the Office of Research, following established procedures and working in conjunction with the Medical Director's office, to accept $25,000 for a 12-month professional services contract from the National Institute on Alcohol Abuse and Alcoholism under which APA would provide statistical summaries of characteristics of psychiatrists who treat alcohol-related problems and of the patient populations under their care (March 1990).

2. Approved as APA policy the concepts expressed in "Statement on Use of Animals in Research" (Sept. 1989).

3. Authorized distribution of "Statement on Use of Animals in Research" to the entire membership, with a cover letter stating the importance of animal research, and allocated approximately $3,500 from the Board contingency fund to supplement Council of Research funds for this mailing (Sept. 1989).

4. Approved the full task force report on benzodiazepine dependence, toxicity, and abuse as an APA task force report (June 1989).

5. Adopted the "Policy for Release of APA Professional Activities Survey (PAS) Research Data" (June 1989).

6. Authorized the Council of Research and the Task Force on DSM-IV to receive, through the Office of Research, funding from the John D. and Catherine T. MacArthur Foundation and NIMH for *DSM-IV* field trials, following established procedures and working in conjunction with the Medical Director's office (Sept. 1989).

7. Approved the report of the Task Force on Electroconvulsive Therapy (ECT) for publication as an APA task force report (2), with changes to the section on ECT for children and with additional references (Dec. 1989).

8. Authorized the Office of Research to seek outside funding from the van Ameringen Foundation, Inc., for its research activities, following established procedures and working in conjunction with the Medical Director's office (June 1989).

9. Ratified the Executive Action taken by the President, Speaker, and Acting Medical Director to authorize the Office of Research to accept a professional services contract from the NIMH Division of Biometry and Applied Sciences, Biometric and Clinical Applications Branch, to organize a meeting on mental health services research to be held during the 1990 APA annual meeting (Sept. 1989).

10. Ratified the Executive Action taken by the President, Speaker, and Acting Medical Director to authorize the Office of Research to accept a professional services contract from the NIMH Division of Biometry and Applied Sciences, Biometric and Clinical Applications Branch, to analyze current data from the Professional Activities Survey and to provide statistical summaries of characteristics of the patient populations under treatment by U.S. psychiatrists (Sept. 1989).

11. Authorized the Office of Research to participate in a joint Harvard-APA analysis of data from the Professional Activities Survey, to be funded by a supplement to an existing NIMH-funded R01 grant to Harvard University; further, authorized the Office of Research to receive $29,667 for its participation in the project, following established procedures and working in conjunction with the Medical Director's office (March 1990).

12. Ratified the Executive Action taken by the President, Speaker, and Acting Medical Director to authorize receipt of $5,000 from ADAMHA to support an expanded mailing of the *Psychiatric Research Report* (Sept. 1989).

13. Ratified the Executive Action taken by the President, Speaker, and Acting Medical Director to authorize the APA Offices of Research and Psychiatric Services to submit a bid to NIMH for a contract to develop a resource manual addressing clinical issues attendant to psychopharmacologic treatments for mental illness from the perspective of the treatment professional (Sept. 1989).

14. Authorized the Committee on Research Training, following established procedures and working in conjunction with the Medical Director's office, to seek outside funding of a conference to promote training programs for psychiatrist-researchers and to facilitate communication among trainees, trainers, researchers, and administrators (Dec. 1989).

Telephone Access

1. Endorsed establishment of free-to-user telephone access to APA offices for members of the Assembly and components, after staff has conducted a feasibility study and explored all appropriate options (June 1989).

2. Approved the Managed Care and Utilization Review Information Line (an 800 number) within the Office of Economics for immediate response to members' needs, with the understanding that funding and staff are to be provided in the 1990 budget (March 1990).

REFERENCES

1. Karasu TB (ed): Treatments of Psychiatric Disorders: A Task Force Report of the American Psychiatric Association. Washington, DC, APA, 1989

2. The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging: A Task Force Report of the American Psychiatric Association. Washington, DC, APA, 1990

3. Scheidemandel P (ed): The Coverage Catalog, 2nd ed. Washington, DC, American Psychiatric Press, 1989

4. Economic Fact Book for Psychiatry, 2nd ed. Washington, DC, American Psychiatric Press, 1987

5. Position statement opposing mandatory name reporting of HIV-seropositive individuals (off acts). Am J Psychiatry 1990; 147: 541

6. Guidelines regarding psychiatrists' signatures (off acts). Am J Psychiatry 1989; 146:1390

7. Guidelines regarding possible conflict between psychiatrists' religious commitments and psychiatric practice (off acts). Am J Psychiatry 1990; 147:542

Report of the Treasurer

Alan I. Levenson, M.D.

General

This report is prepared from audited figures for the fiscal year that ended Dec. 31, 1989. The data presented also appear in the auditor's annual report.

Table 1 is a statement of our financial condition, taken from the independent auditor's report, and table 2 presents functional revenues and costs. These will provide the membership with the information needed to assess the operation and financial condition of the Association.

Fiscal Status as of Dec. 31, 1989

During 1989, APA's general fund operations continued their strong programmatic and fiscal performance. General fund operations in 1989 resulted in income of $24,726,542 and expenses of $23,925,330, for a surplus from operations of $801,212. Of this amount, $300,000 had been included in the 1989 budget for debt reduction. The remaining $501,212 represents surplus beyond that called for in the operating budget.

In 1989 the Association was unsuccessful in its attempt to secure a new and expanded CHAMPUS contract for peer review services and in efforts to establish a commercial peer review program. APA realized a loss during the year amounting to $2,215,279 in conjunction with the termination of these quality assurance activities. When the strong performance of APA's general fund operations is combined with the loss from quality assurance activities, the resulting deficit from total 1989 operations amounts to $1,414,067.

Services for members. APA's most important function is service to its members. Our membership increased from 25,345 at the end of 1979 to 36,208 at the end of 1989, for an average net gain of over 1,000 members per year. The overall increase in the last 10 years was 42.9%, but this growth rate is not equally distributed among the various categories of membership: the number of Members-in-Training (residents) has grown by 284%, General/Associate Members and Fellows have increased by 15%, and members granted Life status (dues-exempt) have increased by 86%. The enrollment and continuing membership of medical students and residents have important implications for the future growth and strength of the Association.

APA began enrolling Medical Student Members in 1984. Since then, membership in that category has grown from 208 to 739, and it now accounts for 2% of the total membership. Medical students are becoming an important source of new Members-in-Training: 103 medical students were advanced to this status in 1987, 136 in 1988, and 148 in 1989.

There are currently 5,848 Members-in-Training, representing 16.1% of the membership. Residents are fast becoming the most important source of new General Members; while the number of new General Members each year tends to remain stable, the proportion of those who become General Members by advancement has grown significantly, from 56% of new General Members in 1984 to 78% in 1989. For example, 820 Members-in-Training were advanced in 1987, 922 in 1988, and 1,070 in 1989.

Our increased membership, our strong financial base, and the increasingly complex problems and opportunities facing our profession have led to expanded services for APA members. This growth in services has been primarily in the areas of government relations, public affairs, education, Office of Membership Services activities, economic affairs, and research.

Net worth. The Association's stated net worth has increased from approximately $4 million in the mid-1970s to approximately $9.7 million today ($9,697,336). This stated figure is extremely conservative, since it does not include the estimated increase in the value of the 1400 K Street property, which APA purchased in 1980. If this estimated increase in land value were to be included as part of APA's stated net worth, the figures would stand at about four and one-half times our net worth in the mid-1970s. Even with the impact of inflation, the increase in the Association's net worth is particularly impressive over the past few years: from $7,486,501 in 1984 to $9,697,336 in 1989, despite a deficit from 1989 operations.

Debt reduction. During 1985 APA negotiated an excellent loan package with the National Bank of Washington and has since renegotiated even more favorable terms. Highlights of the loan package as it is currently configured are as follows:

1. *Term loan*—$1,500,000 at ¾% over the prime rate. As of Dec. 31, 1989, $1,275,000 of the loan had been retired, leaving a balance to be repaid of $225,000.

2. *Line of credit*—maximum of $4,000,000 at ¼% over the prime rate. The stability of the cash budget was evidenced by the fact that the line of credit was used during only 4 months of 1989 and only $2,750,000 needed to be used.

The term loan is scheduled to be completely retired as of September 1990, so APA will meet the most conservative definition of being debt free. However, another debt reduction bench mark has already been met on schedule. As originally projected, the Association's short-term investment portfolio exceeded the term loan balance in December 1987. The bench mark is significant since it represents the point at which it was possible for APA to repay the entire loan from proceeds of the short-term portfolio. The Association has met its obligations under the loan package since its inception.

TABLE 1. APA Balance Sheet as of Dec. 31, 1989 and 1988

	Amount (dollars)	
Item	1989	1988
Assets		
Current Assets		
Cash and cash equivalents	1,325,966	3,151,536
Marketable securities	651,416	651,533
Accounts receivable, less allowance for doubtful accounts	1,234,876	1,492,767
Grants and contracts, approved and in process	1,482,399	2,190,029
Notes receivable	94,500	395,000
Advances to affiliates	799,461	210,732
Publications inventory	523,027	494,111
Prepaid expenses and other current assets	362,063	348,214
Total current assets	6,473,708	8,933,922
Property and equipment		
Land	5,187,470	5,187,470
Building—leasehold interest and improvements	6,986,914	6,884,724
Furniture and equipment	2,393,309	2,262,249
Subtotal	14,567,693	14,334,443
Less accumulated depreciation and amortization	2,367,819	1,939,439
Total property and equipment	12,199,874	12,395,004
Other assets		
Notes receivable, less current maturities	130,500	330,173
Deferred expenses, net of accumulated amortization	2,218,591	1,612,431
Deferred land rent	765,004	724,182
Nonmarketable securities	75,000	125,000
Intangible pension asset	224,324	—
Total other assets	3,413,419	2,791,786
Total assets	22,087,001	24,120,712
Liabilities and fund balances		
Current liabilities		
Current maturities of long-term debt	225,000	300,000
Accounts payable	2,174,850	1,863,666
Accrued expenses	1,824,206	1,780,539
Advances from affiliate	—	306,943
Deferred revenue	1,192,574	2,288,598
Deferred amounts		
Restricted—grants and contracts	705,640	334,862
Restricted—awards and special projects	1,600,527	1,461,160
Total current liabilities	7,722,797	8,335,768
Other liabilities		
Long-term debt, less current maturities	—	225,000
Capital lease obligation, less current maturities	4,442,544	4,455,018
Accrued pension cost	224,324	—
Total other liabilities	4,666,868	4,680,018
Fund balances		
Unappropriated	5,428,304	6,842,371
Appropriated	150,000	150,000
Building	4,119,032	4,112,555
Total fund balances	9,697,336	11,104,926
Total liabilities and fund balances	22,087,001	24,120,712

TABLE 2. APA's Functional Revenues and Costs for Fiscal Years 1989 and 1988

Item	1989	1988
Functional revenues		
Percent from each function		
Publications		
Advertising	15.97	16.02
Subscriptions and related fees	5.65	6.31
Book sales	17.50	22.07
Member services		
Dues from members	34.58	33.90
Meetings income	12.05	9.83
Other income related to member services	2.31	2.75
Other income (investments, overhead on grants, etc.)	11.94	9.12
Total revenues (dollars)	24,726,542	22,244,937
Functional costs		
Percent for each function		
Governance and member component activities (Board of Trustees, Assembly, joint commissions, councils, and components)	14.52	15.41
Publications (APA journals and book sales)	28.99	34.27
Public affairs (public information and government relations)	10.10	10.30
Member services (membership services and educational programs)	24.44	26.33
General administration	13.48	13.69
Abandoned project	8.47	—
Total costs (dollars)	26,140,609	21,823,678

Internal Revenue Service Audit

In December of 1989, APA concluded its audit with the U.S. Internal Revenue Service (IRS) for the taxable years 1985 through 1987. The initial tax assessment sought by the IRS was approximately $1.5 million and related primarily to display advertising. The final tax assessment imposed by the IRS, based on a compromise agreement, was $177,890 for the 3-year period. In addition, APA's tax-exempt status under Internal Revenue Code Section 501(c)(3) remains intact.

Investments

The Investment Advisory Committee has guided the Association's investment program over the last 14 years. The stated investment policy of the Association is "to employ sound investment vehicles affording maximum return consonant with safety of capital, i.e., the type of investment a prudent individual would seek." Given this policy, safety of capital has been identified as the first objective of the investment program. In 1980 the Association carefully reviewed its investment alternatives and shifted a majority of its investment resources from ownership of securities to a dominant ownership position in the new headquarters building. The investment portfolio, as distinguished from the investment in the APA office building, currently stands at approximately $650,000.

The current policy of the Association is to balance investments between debt instruments and common stocks. The market value portfolio valuation of Dec. 31, 1989, indicates the following approximate percentages: 64% in debt instruments, 1% in cash and accrued interest, and 35% in stocks. The Association's investment portfolio is under continuing review and is subject to change in response to changing market conditions.

Publications

Psychiatric News generated income of $3,250,865, contrasted with expenses of $1,467,215, for a surplus of $1,783,650. This amount is $637,970 more than the budgeted surplus of $1,145,680.

The *American Journal of Psychiatry* produced revenues of $2,488,675 and incurred expenses of $1,815,985, for a surplus of $672,690. This total is $208,491 more than the budgeted surplus of $464,199.

The journal *Hospital & Community Psychiatry* realized revenues amounting to $1,035,479 and expenses of $826,848, for a surplus of $208,631. This amount is $165,537 more than the budgeted surplus of $43,094.

The Association and its publishing affiliate, the American Psychiatric Press, Inc. (APPI), maintain approximately 250 book titles in inventory. Total income for the APA publication program (excluding APA periodicals) amounted to $6,536,584. Of this total, $4,327,037 was provided by sales of APA publications and products and $2,209,547 was accounted for by sales of APPI books and products.

A Note of Caution

For the past 2 years my Treasurer's reports to you have contained a note of caution. In essence, I reported that the strong fiscal position of the Association at the end of 1987 and 1988 did not mean that we could relax our efforts in sound fiscal planning, effective program management, and vigorous monitoring of expenditures. The point was that the same hard work which enabled the Association to achieve its stable financial situation was needed to maintain it.

As discussed earlier in this report, a deficit from operations in 1989 has reduced, but not eliminated, the Association's financial strength. Income from products and services is difficult to project, and dues income cannot be used as the basis for organizational growth in the future. The economic literature provides empirical evidence that our national economic environment is becoming in-creasingly unpredictable, and we know that our professional environment is fraught with change and uncertainty. These factors reduce the extent to which we can have confidence in even the most sophisticated long-range plan. Planning continues to be necessary, but with this ongoing planning we must maintain our ability to respond quickly to the professional and fiscal challenges facing us.

Conclusion

APA has developed a sound financial position over the course of many years. Much of that strength has stemmed from programs supported by our general fund, which have not only provided many needed services for our members and our patients but also have generated enough income to more than cover the cost of the services.

Our fiscal strength has also been bolstered by APPI, Professional Risk Management Services, and our building program at 1400 K Street, N.W., Washington, D.C. During 1989 one of our ventures—the effort to expand the Quality Assurance Program—proved to be unsuccessful. An important point in this regard is that, while the results from this program dampened our fiscal strength, we retain sufficient financial wherewithal to field an impressive array of programs, to meet current obligations, and to maintain a significant net worth. An even more important point is that the Association must not allow this result to reduce its will to pursue, when feasible, ventures having a positive potential for the field of psychiatry, even where risk is involved. We have a good batting average in this regard and the potential for future successes.

It will be necessary for APA to continue its thoughtful approach to conducting the affairs of the Association. Priority setting will remain a key factor in our success, since our members and staff will always have more good ideas than the budget can support. These same pressures also point to the need to bolster nondues income and to carefully monitor expenditures.

I am delighted to have had the opportunity to serve as your Treasurer and look forward to working with you in moving APA further toward its goals in the future.

Report of the Medical Director

Melvin Sabshin, M.D.

During my 16-year tenure as Medical Director of APA, the annual report has become a useful reflection of progress and problems. We have indeed been coping with extraordinary challenges; the themes of socioeconomic and political ferment have dominated my reports for some time. The coping process has been accompanied by a steady growth in our membership and an increase in the diversity and complexity of the functions assumed by the national leadership and the Central Office. Since last year's report, we have faced many difficult decisions and actions, and I am pleased with the mood, strength, stability, productivity, and responsiveness of the organization. Both the tone and content of our activities are positive overall and demonstrate strong effective working relationships between staff and members. Dr. Herbert Pardes' thoughtful, energetic, and effective leadership is reflected in the strength and enhancement of many departments' efforts.

While the quantity of work at the Central Office continues to increase, we have been able to maintain quality, even in the face of increased demands in many arenas. This year, the Association has focused on how to provide the best support and leadership for the diverse needs of more than 36,000 members while avoiding the fragmentation that could result from increased interest in subspe-cialization and a variety of forms of practice. We also have been concerned with the impact of the termination of our Quality Assurance Program and its effect on our fiscal and substantive functions. We have carefully monitored our business-related work, as well as the more traditional specialty society efforts. To that end, we have held frequent discussions with our counterparts in other medical specialties and in the other mental health disciplines.

Staff changes highlight the balance between stability and growth, gains and losses. In December 1989, APA's Librarian, Ms. Zing Jung, retired after more than 9 years of service to the Association. Ms. Jung was a remarkable leader in our communication and information processes. Under her guidance, the Library became a modern storehouse of information with computerized data bases and audiovisual learning materials, in addition to books and journals. She was widely recognized as a leader in her field, and her support of the Marion E. Kenworthy Learning Center was key in establishing this computer and videotape resource for members and staff. I have appointed Mr. William Baxter, Archivist, as the Interim Director of the Library, and we look forward to working with him in his new capacity, as well as in his previous role. As we approach our sesqui-

centennial, the integration of our history with advances and plans for the future will be increasingly important.

After an extensive search, Ms. Andrea Morgan was appointed Director of the Office of Resource Development in October 1989. Her first months on staff have been extremely productive. She has worked with the Resource Development Committee to prepare a strategic plan and begin its implementation. Specifically, we have written to newly elected Life Members and Fellows as the first stage in our member-related efforts and also have contacted foundations about support for special projects and activities.

Another change is the resignation of Ms. Ellen Smith, who is moving to New Jersey to join her husband as he moves to a new job. Ms. Smith has been an invaluable resource for the Division of Government Relations, providing excellent staff support in many areas but especially in our work related to the resource-based relative value scale. She also has been the staff liaison for the Council on Aging and its components. Her contributions have been outstanding.

The largest and most painful staff change, however, has been related to the termination of the Quality Assurance Program. On the basis of CHAMPUS's review of our initial response to its request for proposals, APA was one of three organizations given the opportunity to prepare a "best and final offer," which was submitted to CHAMPUS in August 1989. In late September, we learned that another organization, Health Management Strategies of Washington, D.C., had been chosen. Needless to say, we were most disappointed with the CHAMPUS decision. Although we had prepared an excellent proposal, our bid of more than $30 million for the 5 years of the contract was considerably higher than that of the awardee. APA costs were higher, in part, because of our commitment to quality review and the involvement of qualified mental health professionals in the decision-making process.

Never before in our history has there been termination of a function of such magnitude, nor the loss of so many staff through the considerable reduction-in-force that accompanied the conclusion of the project and of our review functions. These losses—which included highly trained review specialists, long-time employees, and psychiatrists (APA members)—have caused considerable anxiety and concern among staff and members. It was a relief that most staff who so desired were employed by local review groups, and the market for such highly trained personnel is good. Nonetheless, these efforts have tested our coping skills. Dr. John Hamilton, Deputy Medical Director and Director of the Office of Psychiatric Services, and his staff deserve our appreciation for their productive work over the years and in the termination process, and I want to express my appreciation to Deputy Medical Director Dr. Carolyn Robinowitz for her leadership in the transition and to Mr. Charles North and the Office of Personnel for their extraordinary efforts.

This change also has had an impact on our overall finances and budget implementation. A long history of careful fiscal planning and care in expenditures this year have ameliorated the damage, but much of our work this year has addressed the related difficulties and impact on morale.

While our involvement in quality assurance efforts generated much discussion and no small amount of controversy over the years, I have been impressed by the positive response of colleagues and policymakers to these efforts. They believe that quality assurance review is documentation of the scientific base of psychiatric care and that it can be monitored to provide cost-effectiveness. Such a view does much to offset the myth that psychiatric care is subjective, interminable, and costly, and it promotes access to quality care and helps ameliorate stigma.

There is currently considerable interest in organized medicine in the development of practice parameters—standards and guidelines. The Council of Medical Specialty Societies is sponsoring conferences and other educational activities related to standards development, and the American Medical Association (AMA) has undertaken a major project in which specialty societies can address the topic. Drs. Edward Hanin, John Hamilton, Harold Pincus, Carolyn Robinowitz, and Sara Charles have represented us in these endeavors and are optimistic about the ways we can work with other medical specialties and about the potential impact of such efforts. Our own efforts will be led by the newly appointed Joint Board and Assembly Work Group on Practice Parameters (John McIntyre, M.D., chair-

person). The committee will participate in other such efforts and will use such materials as the APA task force report on ECT (1) and the book *Treatments of Psychiatric Disorders* (2). This book has received much praise and been referred to as a "remarkable" and "scholarly" volume. Dr. Seymour Halleck (3) referred to it as "the best psychiatric book ever," stating that APA members "have every reason to be proud of it. While the American Psychiatric Association has made many memorable contributions since its inception, the production and publication of *Treatments of Psychiatric Disorders* may represent its finest and most selfless accomplishment. A hundred years from now, when historians are writing about the treatment of mental illness, 1989 will be cited as a landmark year in which a medical classic was published."

There continues to be considerable interest in the governance process. The increased activities of the Assembly Executive Committee and its evolution as a major force in the governance of the Association were reflected in its interim meeting in September 1989, its second successful joint meeting with the Joint Reference Committee in February 1990, and its expanding role in helping the Assembly plan and implement actions. The Joint Reference Committee, too, has strengthened the input of its voting members while maintaining the importance of the participation of council chairpersons, emphasizing its role as "joint," representing both the Assembly and the Board. The Joint Reference Committee increasingly acts not simply as a referring body, but also as an initiator and developer of proposals and directions. Drs. Elissa Benedek, Edward Hanin, and Bernice Elkin are to be congratulated for their thoughtful yet pragmatic approach to both issues and processes. Ms. Claudia ("Corky") Hart, Associate Director of the Office of Psychiatric Services, has been a marvelous resource here, and the outstanding work of Ms. Jeanne Robb and the other staff of the Office to Coordinate the Board and Assembly makes the process work smoothly.

Discussions about the roles of officers and trustees reflect the increased involvement and interest of Board members, the expanded amount of business on the agenda of each meeting, and the need to set aside time for reflection and strategic planning for the Association. This interest in organization and function is reflected in the ongoing discussion of subspecialization and liaison activities by the Assembly and ad hoc committees of the Board. The Ad Hoc Committee on Liaison Activities sponsored a second meeting of leaders of key psychiatric organizations, which was chaired by Past President Paul Fink, M.D., and held during the fall component meetings. The meeting itself was well attended, and participants' recommendations have formed the basis for much work since. The American Board of Psychiatry and Neurology (ABPN) responded positively to our recommendation that it offer a certificate of added qualifications in geriatric psychiatry and is holding a meeting this summer to consider the possibility of similar certification in addictive disorders. While continuing to explore these issues, we will be cognizant of the potential fragmentation and divisiveness of such efforts and the need to maintain organizational strength while maximizing input from all concerned.

I am very enthusiastic about the formation of the new Council on Addiction Psychiatry, chaired by Dr. Roger Meyer, who brings leadership in research, clinical care, and education to the task. I also appreciate the special efforts of Ms. Hart in the planning for this council.

This summer, staff of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) proposed that state hospitals again be surveyed according to the *Consolidated Standards Manual* rather than the *Accreditation Manual for Hospitals*. The *Consolidated Standards Manual* gives more attention to psychiatric facilities but does not require medical leadership. We strongly opposed this change, noting that hospital-based standards should be used for psychiatric units in both general hospitals and psychiatric hospitals, and medical oversight is basic to high-quality care. We were concerned that a change in accreditation standards for state facilities may ultimately result in lower standards of care for patients in these facilities, and we emphasized review of all practices, including 1) development of additional standards in such areas as ambulatory care, psychosocial rehabilitation, and psychiatric care in managed care settings and 2) the appropriate training of surveyors. Dr. Hamilton, Ms. Hart, and Mr. Justin DeSua, Programs Coordinator in the

Office of Psychiatric Services, coordinated the work of our representatives to the JCAHO on this issue, which demanded considerable time for negotiations with representatives of the National Association of State Mental Health Program Directors and the JCAHO. Our meeting with JCAHO President Dr. Dennis O'Leary and JCAHO staff was very productive in this regard.

We also have been actively assessing the impact of managed care and developing approaches to this issue. This task has been an interdepartmental staff effort coordinated by Dr. Robinowitz and involving staff in the Office of Psychiatric Services, Division of Government Relations, Office of Economic Affairs, and Office of Public Affairs, who have been working with the Ad Hoc Committee on Managed Care, chaired by Dr. Steven Sharfstein. A similar interdepartmental effort has dealt with the release of clozapine and the special circumstances of access to that drug. Dr. Hamilton took the lead in arranging for a special forum at the annual meeting to discuss issues related to clozapine's release.

I am most gratified with the direction provided by Dr. Allen Frances, who chairs the Task Force on DSM-IV. During the past year, there has been an extraordinary amount of activity in this area, and various work groups have been most productive. The third edition of *DSM-IV Update* provides excellent information on process and content. The oversight Committee on Psychiatric Diagnosis and Assessment within the Council on Research, chaired by Dr. Layton McCurdy, provides policy direction and leadership. Dr. Frances continues to meet with the Assembly, the Board of Trustees, and other member components to report and receive input. Dr. Harold Pincus and the staff of the Office of Research have been invaluable in providing coordination and support for these important activities. The process has focused on the best integration of research and clinical directions in nomenclature and diagnosis; by providing representation and oversight throughout, we hope to maintain a high degree of member involvement.

Dr. Pincus and his staff have received much praise from the field for the quality of *Psychiatric Research Report*. This quarterly newsletter provides considerable information about science policy, funding and educational opportunities, and research programs. Also, the yearly brochure addressing appropriations for the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) has been extremely useful in our educational efforts.

Congratulations also are due Dr. Pincus for his extraordinary efforts in obtaining significant funding from the National Institute of Mental Health (NIMH) and private foundations to support research and field trials related to DSM-IV. In addition, funds have been obtained from the van Ameringen Foundation for activities designed to improve the recruitment, training, and retention of psychiatrist researchers. Additional congratulations are due Dr. Pincus and Dr. Jeanne Spurlock, Deputy Medical Director and Director of the Office of Minority/National Affairs, for their success in implementing a program, funded by a grant from NIMH, to support research training for minority psychiatrists.

The *American Psychiatric Association Biographical Directory 1989* is widely utilized. Dr. Thomas Dial and the staff of the Office of Survey Design and Analysis are now planning extensive analysis of the associated survey on professional activities. These data are important in outlining the current shape of the field and will be a base for future planning.

In previous annual reports, I have given special emphasis to our activities in government relations and public affairs. This year is no exception; indeed, I still rate these areas as having the highest priority because of their ability to diminish stigma and increase access to and reimbursement for care. Working in concert with the Joint Commission on Government Affairs, Dr. John J. McGrath, chairperson, and the other commissioners and network leaders, the Division of Government Relations continues to be a sophisticated, effective force.

From my perspective, during this past year we have been much more visible and successful in our government relations activities than ever before. We have begun to develop clear and concrete objectives, which have had an enormous impact on our members and the patients we treat.

This year, the Congressional Conference Committee increased ADAMHA funding significantly; the total funding approved for

NIMH research is $64 million greater than in the previous fiscal year. In an even more unprecedented move, in spite of major budgetary cutbacks Congress removed the discriminatory outpatient dollar limitation on the Medicare mental health benefit. While the bill also included a provision for direct reimbursement of psychologists and social workers, we were successful in obtaining a Congressional mandate for medical consultation for patients who are being seen by these nonphysician providers. This action was vigorously but unsuccessfully argued against by psychologists, who recognized the symbolic as well as concrete message regarding physician involvement and who have become aware of the nuances of our continuous reinforcement of the importance of physician involvement in medical differential diagnosis and treatment planning for this special population.

These actions point out the immense effectiveness of our educational efforts and the impact of the scientific advances in the field on Congress's willingness to fund more equitably. They document the importance of an integrated approach, rather than support of just one aspect of the research/education/care continuum. They also represent the fruits of many years of ongoing efforts on the part of our Division of Government Relations staff and APA members.

Recently staff has worked with members of the Mental Health Liaison Group to develop a budget for ADAMHA appropriations based on professional judgment; the group has begun a lobbying effort involving research scientists, clinicians, and patient advocates to promote this budget. We also are monitoring closely the Bush administration proposal for an $8.1 billion cut in Medicare spending, reductions in federal spending for medical education, and lower hospital reimbursement rates. Additionally, we are working with the staff of Congressman Gary Ackerman (D-N.Y.) on the mental health benefits in his proposal for federal employees' system-wide health benefits.

We are most fortunate to have Mr. Jay Cutler leading our government relations efforts. He is widely respected not only on Capitol Hill and in the administration, but by his colleagues as well. Our successes are a credit to his energy and knowledge and to the long-range strategic planning and involvement of the field in Congressional communications.

This year has seen a continued increase in the amount and contentiousness of American Psychological Association efforts to expand the scope of practice and the services provided by psychologists. In mid-April the California Supreme Court heard oral arguments in *CAPP v. Rank*, which concerns hospital admitting privileges for psychologists; a decision is expected within 90 days. In addition to *CAPP v. Rank*, we have seen attempts in state legislatures to add hospital privileges to psychologists' scope of practice. Further, the attempt to gain privileges for prescribing psychotropic medications—supported in part by consideration of a pilot study of such practice by the U.S. Department of Defense—has raised serious concerns about the potential impact on patient care. No matter how collaborative individual interdisciplinary professional relationships have been, psychiatrists, who are aware of the potential problems, side effects, and interactions of psychotropic medications and the need for medical planning and oversight, uniformly express horror at the possible involvement of insufficiently trained personnel in prescribing.

I recently had the privilege of representing APA at a meeting of military health care staff and representatives of the health and mental health community that was held in response to a directive of the Subcommittee on Defense of the U.S. House of Representatives Committee on Appropriations. The subcommittee stated that the demonstration program involving medication prescription by psychologists could not go forward until Congress had reviewed the educational curriculum and training program developed by the Department of Defense. My position was straightforward: no one should prescribe and monitor medications for patients with mental disorders without the appropriate theoretical and practical medical education.

The American Psychological Association has been most vocal in supporting this expansion of psychologists' scope of practice, stating that this area of practice policy has the highest priority, although its members are divided as to its extent. It is ironic that at the same time psychologists are attempting to gain prescribing privileges, they

strongly espouse *psychological*, as opposed to psychopharmacological, care and are quick to point out some of the problems in using medications. As one example, the brief they filed in *Harper v. Washington State* cited the danger of treatment with drugs that can "disfigure and disable a prisoner."

I am optimistic that the appointment of Dr. Raymond Fowler as the Executive Officer of the American Psychological Association will set the stage for better communication and possible negotiation. Additionally, we have had good contact with the officers and staff of the newly formed American Psychological Society. This organization of psychologist-scientists has grown considerably, and its leaders share many of our concerns.

We continue to be impressed with the creative leadership of Dr. Lewis Judd, who has completed his second year as Director of NIMH. He has a wealth of experience and leadership in the research arena and sensitivity to future needs. Last year, Dr. Judd, in collaboration with the National Mental Health Association, initiated a National Mental Health Leadership Forum, whose members represent major professional organizations and advocacy groups. In conjunction with the National Advisory Mental Health Council, this group held a meeting and hearings in Marshall, Minn., in early April; their efforts did much to identify needs, minimize stigma, strengthen the process for planning efforts to improve access to and organization of care, and determine the base for the proposed "war on mental illness" supported by the National Mental Health Leadership Forum.

Our representation to the AMA has been strong. Our delegate, Dr. John McGrath, and alternate delegate, Dr. Richard Steinhilber, have worked with the Section Council on Psychiatry and with other members of the House of Delegates to support both ideas and resolutions. Dr. Steinhilber, through his membership on the Council on Scientific Affairs, has been able to influence areas of AMA scientific investigation. The addition of the American Academy of Child and Adolescent Psychiatry and our representation in the Resident Physicians' Section and Young Physicians' Section have been productive. We are awaiting the final version of the AMA Council on Long Range Planning's report on the future of psychiatry. Dr. McGrath's excellent contributions have been evident in his membership on the AMA Council on Legislation and his leadership of reference committees. Although we were disappointed by the outcome of his candidacy for the AMA Board of Trustees, the opportunity and visibility were important for him and for the field.

While our work on the *Physicians' Current Procedural Terminology (CPT)* is still to be accepted by the AMA *CPT* editorial panel, we are continuing our educational efforts and negotiations. Mr. Cutler has worked most effectively with AMA staff in the legislative arena, and I have enjoyed and profited from my meetings with AMA and other specialty society staff. I was, of course, distressed at the circumstances leading to Dr. James Sammons's resignation. Not only do such events weaken the association, but over the years I was impressed with Dr. Sammons's knowledge and strong leadership and am disheartened at the outcome. Dr. James Todd, the Senior Deputy Executive Vice-President, has assumed the acting position, and a search is under way for Dr. Sammons's successor. We will watch the process closely, as we hope to continue our positive and effective interactions with AMA staff.

We have been quite successful in our public affairs functions. In his capacity as chairperson of the Joint Commission on Public Affairs, Dr. Harvey Ruben has provided energetic and wise leadership, working with Mr. John Blamphin, who heads our staff division. Collaborative projects with industry have helped enhance psychiatry's image with other physicians and the public. The joint effort with the Upjohn Company has supported several APA productions. The first film produced in this venture, "Panic Prison," has been well received by viewers. The Washington, D.C., premiere of the second film, "Faces of Anxiety," took place at the Kennedy Center on May 2, in cooperation with the National Mental Health Association and in recognition of May as Mental Health Month. Efforts are under way to develop the third film, which will be on depression. We now have an experienced network of trained leaders who can effectively use all varieties of media.

We are continuing our campaign against stigma. Mental Illness Awareness Week has become a major year-round national effort; it

is an outstanding model for interdepartmental and interorganizational collaboration and highlights the importance of work with consumer advocacy groups. This year there was a considerable increase in publicity and in interest by professionals, the media, and the public.

The very successful symposium "Advances in Research and Clinical Care," chaired by President Pardes, was held on Capitol Hill and attended by a standing-room-only crowd of Congresspersons, staff, and community representatives. Planning for 1990's Mental Illness Awareness Week is already well under way, and we hope to continue the expansion of activities and coverage, both nationally and at the local level.

Many public affairs efforts this year have disseminated information to the public and the profession. In addition to proactive efforts, we have responded to the San Francisco earthquake and Hurricane Hugo. These tragedies have brought out the best in our members in their work with the communities they serve. Members responded strongly to Ann Landers' attack on psychiatrists; her personal comments and her published apology indicated that we did have an impact.

Dr. Robinowitz and Dr. John Talbott were successful in obtaining funds from the Pew Memorial Trust to support a series of activities aimed at increasing collaboration between academic departments of psychiatry and state mental health programs. The project director, Ms. Ruth Pitlick, has developed an excellent newsletter outlining project objectives, future actions, and current successes.

Our AIDS Education Project, under the leadership of Ms. Carol Svoboda, has developed a series of excellent educational activities and materials. In collaboration with our Commission on AIDS, chaired by Dr. Stuart Nichols, and with staff support from Ms. Jackie Moore, the AIDS Education Project has completed an excellent videotape that deals with attitudes as well as cognitive information. Project efforts have been most important in addressing the problems of HIV disorders and the special stigma affecting AIDS patients.

We are pleased with the many activities of the Office of Education, which promote continuing education for our members. Dr. Philip Bashook and his staff have worked with district branches and other organizations to ensure that programs are well planned and organized. There has been considerable effort to develop self-learning and self-study programs, as well as formal learning opportunities. Most noteworthy has been the *Psychiatric Knowledge and Skills Self-Assessment Program (PKSAP)*. The final module of the sixth edition was recently published, and I recommend it to you as an excellent opportunity to evaluate and update your knowledge at your own pace, at a time and setting of your choice.

We also appreciate the special attention and support provided to residents through the Office of Education and, in particular, Ms. Rosalind Keitt's coordination of activities and components addressing resident issues. This work is increasingly demanding and complex, given the growth of resident members in the Association and their increasing presence in its governance system.

Of our more than 36,000 members, over 5,300 are residents. This was the second year in which the Board of Trustees has included both a Member-in-Training Trustee and Member-in-Training Trustee-Elect. There has also been increased active resident participation in the Assembly and area councils. A component for/on young psychiatrists was established; it interacts with its companion component of young physicians in the AMA and addresses the particular needs of younger psychiatrists and issues related to their practice. Our retention of residents following training is excellent, and the Board of Trustees demonstrated awareness of special issues for this population by adopting a graduated dues schedule for the first years after residency training.

Our yearly census of all psychiatry residents documents the interest of medical students in psychiatry. This year, however, there was a drop in the number and percentage of medical students choosing first-year positions in psychiatry through the National Resident Matching Program. In the upcoming months we will gather more data and try to determine the reasons for this change. Psychiatry residents also noted greater satisfaction with the field (considerably fewer transfer from psychiatry to other specialties) and greater interest in combined residencies or postresidency subspecialty training.

The residents themselves are bright and articulate and bring a special vitality to the Association.

Dr. Marta DeLalla has been a most effective Director of the Office of Membership. She and her staff have made a special effort to recruit and retain members, maintain a strong working relationship with district branches, and provide the highest quality of communication and services to all our members. She and her staff have worked closely with the Ad Hoc Committee on Membership and Fiscal Policies, chaired by Dr. Michael Vergare, and in collaboration with Mr. Rich Feeley, APA fiscal consultant, have prepared an extensive analysis of membership demographic and growth patterns. Our studies of member retention (at all levels) have emphasized the importance of the district branch dues structure in membership stability. We also recognize that some areas of the country are experiencing a "graying" of the membership and an increase in the proportion of members who hold Life status; such district branches continue to provide costly services but without the dues income to support them.

Also gratifying has been the significant number of members who vote in our elections for APA officers and trustees. We remain one of the few large national organizations that conduct contested elections with voting open to all members, and our colleagues in other specialties and disciplines continue to voice their amazement that 40% of our members vote. We were distressed to learn that this year, through a mailing house error, a small number of members in the Seattle area received duplicate ballots. Fortunately, we were able to ascertain that the number of members who received duplicates was small, and no contested office was decided by so small a number of votes as to be jeopardized by the problem. We have received apologies from the mailing firm, which has taken measures to guard against repetition of the problem in the future. I am very appreciative of Ms. Carol Lehmann's attention to the problem and her work with the firm and with Dr. Bernice Elkin and the Elections Committee in addressing the issue. The election process is an enormous task for a group as large as ours, and I am impressed with Ms. Lehmann's careful attention to detail and mastery of the multiple issues that must be considered to assure a fair and accurate election.

While Dr. Spurlock and the staff of the Office of Minority/National Affairs have been active in many areas, providing voice, support, and recognition to minority issues and to those affecting children and families, their contributions to the residents' fellowship programs have been especially meaningful to these colleagues and to those of us who interact with them. We are honored to report that Dr. Spurlock was appointed by the Secretary of the U.S. Department of Health and Human Services, Dr. Louis Sullivan, to the Board of Regents of the National Library of Medicine. Dr. Spurlock also has acted as representative or liaison to medical, mental health, and advocacy groups and has been a most effective spokesperson for the Association.

In response to many letters expressing concern about the timing of the joint meeting with the German Society of Psychiatry and Nervous Diseases, its relationship to Yom Kippur, and both the practical and symbolic aspects of holding the meeting at that time, the meeting schedule was modified such that the joint meeting will begin Monday, Oct. 1, 1990.

Dr. Allan Tasman has been a thoughtful and energetic chairperson of the Scientific Program Committee. Under his direction, the program at the annual meeting continues to increase in scope and sophistication. There has been greater attention to integrating research findings into the scientific educational program and efforts to provide more interactive and participatory sessions for clinicians. The annual meeting is a high point of the year. It is a mirror of directions for the field, as well as a proactive and integrating force. The scientific program theme, "The Research Alliance: Road to Clinical Excellence," and the focus on new directions in the field have generated much interest and excitement. There are multiple sessions and formats and an expanded number of continuing medical education courses. The Local Arrangements Committee, chaired by Dr. Philip Muskin, took advantage of the many opportunities in New York to offer an extremely diverse and stimulating program. Advance registration for the meeting was the highest ever. Joined by members of the Scientific Program Committee and the Local Arrangements Committee, Dr. Tasman has already begun planning for the 1991 meeting

in New Orleans, which promises to be of very high quality as well. We also have begun plans for the 1994 sesquicentennial annual meeting, which will be held in Philadelphia. A staff committee, chaired by Ms. Carol Davis, has been formed and will work with a committee of members to plan significant events related to the sesquicentennial celebration.

None of the success of the annual meeting could have taken place without the devoted efforts of the staff. In particular, I would like to recognize Ms. Davis, who has provided oversight, support, and her special know-how and experience in so many areas. Mr. George Campbell and staff of the Office of Meetings and Exhibits Management have been immensely helpful, and their professionalism has contributed to the positive tone and format. The remarkable organizational efforts of Ms. Cathy Earnest Nash, who heads the Office to Coordinate the Annual Meeting, and her staff provide a smooth, highly organized program. Their creativity, hard work, and resilience enable us to handle this complex, multifunctional, and large-scale event in a way that provides an opportunity for each attendee to have an enjoyable and useful educational and social experience.

We similarly are pleased with the Hospital & Community Psychiatry Institute. Not only did the 1989 Institute in Philadelphia attract a record number of attendees and faculty, who participated in a large number of excellent presentations, but the participants' high degree of satisfaction reflected the depth and diversity of program content and the opportunities for interaction among attendees and presenters. The Institute also included special sessions cosponsored by allied professional organizations.

The *Hospital & Community Psychiatry* journal also has grown in quality and stature and reflects the scientific directions of the field, as well as emphasizes innovative aspects of clinical care. The creativity of Editor Dr. John Talbott is reflected in the various columns that integrate policy and theory with clinical practicality. The excellent working relationship between Dr. Talbott and Managing Editor Ms. Teddye Clayton has been a model of staff and member collaboration. Similarly, the journal provides a positive model of interdisciplinary collaboration.

The *Psychiatric News* Editorial Advisory Board, chaired by Dr. George Tarjan, has been reviewing both the policies and content of the newspaper. Consultants from other publications (e.g., *AM News*) have provided valuable input. Under the leadership of Dr. Robert Campbell, Editor-in-Chief, and Mr. Herbert Gant, Executive Editor, *Psychiatric News* is demonstrating increased emphasis on meeting members' informational needs. A new section, highlighting psychiatrists' accomplishments and interests, and greater editorial focus are planned.

The collaboration between Dr. John Nemiah, the Editor of the *American Journal of Psychiatry*, and Ms. Melanie Shipley, Managing Editor, also contributes to an excellent product. Dr. Nancy Andreasen's appointment as Deputy Editor ensures continuation of the high standards of scientific excellence set by her predecessor, Dr. Morris Lipton. We continue to be positively impressed with the quality and quantity of articles in the *Journal*. The educational review articles particularly are an excellent means of presenting current scientific data. The *Journal* has, through use of technological support, improved the review process and shortened the time between submission and publication.

The APA Ethics Committee has been very active, especially in addressing changes in procedures for investigating ethical complaints. The 2-day workshop held in November 1989 for chairpersons of district branch ethics committees was extremely informative and useful, and we received much positive feedback from participants. Ms. Davis, who provides staff support for the committee, is to be commended for her careful, thoughtful, sensitive, and sensible efforts; we also appreciate the first-rate legal support provided by Ms. JoAnn Macbeth and Mr. Joel Klein. Their workloads have intensified as the demands on the committee and staff have increased both in quantity and complexity. The Subcommittee on Education of Psychiatrists on Ethical Issues is completing a second videotape on undue familiarity between therapist and patient, focusing on treatment and reporting.

We have been very pleased with the development of our Office of Information Systems. Under the leadership of Dr. William More, we have developed innovative approaches to information services for

our members. Our ability to communicate and to collect and retrieve information has expanded immensely. This spring we initiated a "voice mail" system, which will be available to members after the meeting. Callers with touch-tone telephones will be able to obtain information about government relations, education, public affairs, research, etc. We are very proud of the excellent, user-friendly system for registration for the annual meeting and of the ongoing routine computerized work of the Association regarding member communication, dues billing, accounting and financing, and so forth. Dr. More, who is nationally recognized as a medical statistician, has been an excellent resource in our information generation and data analysis. He meets the enormously complicated demands of the business and other aspects of our needs in a creative and supportive manner. We believe that in the future, communication and information will be an increasingly important base for our functions.

I also am mindful of many members and staff who have devoted their energy and wisdom to integration, coordination, and unity. In a very special way, Ms. Jeanne Robb and staff in the Office to Coordinate the Board and Assembly epitomize the many functions carried on within APA. They promote the best in our governance system and ensure strong links between members and staff.

Also deserving of special mention is the sustained, remarkably high-level contribution of Mr. Joel Klein and other members of the law firm Onek, Klein & Farr. We have found them available to us for many activities. I will touch on Mr. Klein's work on professional liability, but he also deserves praise for his work with our Commission on Judicial Action. He has been a valued friend, as well as counselor, through a number of difficult and thorny decision points.

In connection with the Commission on Judicial Action, I must point out that Dr. Paul Appelbaum has been a most effective leader of this component, addressing a broad array of legal and judicial issues.

I have particularly enjoyed being active in the World Psychiatric Association (WPA) and chairing the work group charged to prepare a new structure for the organization. Our Office of International Affairs has expanded its efforts and gained wide respect under the leadership of Ms. Ellen Mercer, and this remains a source of special pride and satisfaction to me. Ms. Mercer and her staff provide assistance for psychiatrists in this country and abroad on issues of education, transcultural practice, and care.

Ms. Mercer was a consultant to the U.S. Departments of State and of Health and Human Services regarding the visit last year of psychiatrists, lawyers, and other experts to the Soviet Union to examine current and former patients involuntarily committed to mental hospitals allegedly for political or religious activities. Their report, issued in the summer of 1989, was most important in the readmission of the official Soviet psychiatric organization, the All Union Society of Psychiatrists and Narcologists of the USSR, to the WPA. After much debate, the All Union Society was accepted into membership on the condition that a site visit by the WPA Review Committee be made in 1 year. If the committee finds that psychiatric abuse has continued, a special session of the WPA General Assembly will be convened to consider suspension of the All Union Society. This action met our major concerns, represents remarkable movement by the Soviets, and was an effective compromise that set the tone for future monitoring and collaboration.

My concern continues to be for the field of psychiatry and our patients, and anything that weakens psychiatry in any country ultimately hurts us as a field. It is time to move past debate and to pay attention to the scientific, social, and economic issues that affect care. I plan to work with the Office of International Affairs and the Council on International Affairs, chaired by Dr. Paul Fink, to increase the dialogue and educational interactions.

I am most gratified by the creative leadership and energy shown by Past President Dr. Carol Nadelson as Editor-in-Chief of the American Psychiatric Press, Inc. (APPI). In the past year she has been extremely active not only in broadening and strengthening the ongoing work of APPI, but also in developing strong working relationships with potential authors in this country and abroad. The APPI Editorial Board has been expanded to include experts in a variety of clinical areas. Under the able guidance of Mr. Ron McMillen, General Manager, APPI has begun publication of journals; this effort will provide an opportunity for leadership in such areas as neuropsy-

chiatry, psychosomatic medicine, psychiatric education, and psychotherapy. Our expanded marketing efforts, coordinated by Ms. Karen Loper, have already resulted in new directions and greater income. APPI's staff work in expanding our foreign markets has resulted in new professional and business alliances plus greater opportunities. In its 9 years of existence, APPI has become widely recognized and highly regarded in the publishing industry. Not only does it have a competitive edge in psychiatric publications, as evidenced by the content of book reviews and by sales volume, but its products also provide an opportunity for scientific education and negation of some of the stereotypes about psychiatry and psychiatric patients.

The crisis in medical liability has been marked by questions about the availability and cost of general liability insurance in this country, and this situation has had a profound impact on many functions and activities. Just a few years ago, we had major problems obtaining needed liability insurance for our members. A separate corporation was formed—Professional Risk Management Services, Inc. (PRMS); by serving as our insurance administrator, PRMS has provided an important, cost-effective service for our membership. As a separate and young corporation, PRMS has faced problems of accountability and availability of insurance for all members and has dealt with issues specific to such areas as administration and general medical care.

In December 1989 we received an offer from one of the four owners of PRMS to purchase the other owners' shares of the company. After careful review and consideration of the legal, fiscal, and service considerations, we agreed to sell our share. Not only did we receive a reasonable return on our initial investment, but we now have greater freedom and control. By not being bound to PRMS but still maintaining control of the APA Insurance Trust and risk management policies, we can make strong demands for excellent service and maintain our freedom to negotiate with PRMS or other administrators for our programs. The APA Insurance Trust remains unchanged, as does our participation in the various policy and procedural aspects of rate setting and risk management. We feel better able to protect our members while ensuring the availability of the most cost-effective insurance programs. Special acknowledgment must be made of the extraordinary efforts of Mr. Klein, APA Treasurer Dr. Alan Levenson, Dr. Robinowitz, our consultant, Mr. Rich Feeley, and the APA members involved in the many insurance committees. Our active efforts in this area have been vital to our members' practices.

Special note also should be made of the contributions of Ms. Elizabeth Thomas, who, in addition to her role as Assistant Director of the Office of Membership, serves as the ombudsperson for APA members in insurance-related matters. Ms. Thomas has developed a strong working relationship with PRMS and has been extraordinarily helpful in addressing and solving problems involving communication and information. Through her efforts, the number and intensity of complaints related to insurance matters has fallen considerably.

Business ventures, such as our work with PRMS, demand both substantive knowledge of issues affecting our members and their practices and a sound fiscal structure. The many business-related activities in which we have become involved are more difficult to predict than our more traditional functions and have demanded a monumental effort, including more staff coordination and proactive planning. I am especially grateful to Dr. Levenson, to the chairperson of the APA Budget Committee, Dr. Steven Sharfstein, and to the many other members who have played key roles in ensuring income for the Association and in regulating our expenses. Dr. Jack White, Deputy Director for Business Administration, Mr. Robert Milanicz, Comptroller, and the staff involved in budget implementation also have done an excellent job.

Mr. David McClanahan has contributed strongly to the smooth day-to-day functioning of my office. Ms. Katherine Chambless has been a marvelous addition to the team. Dr. Robinowitz also has been pivotal in this integrative effort, which, in my judgment, shows APA at its working best. Further, Dr. Robinowitz has consistently taken on increasing responsibilities in all areas of Association functioning and has performed magnificently. As far as I am concerned, our working partnership in day-to-day and long-range management is excellent.

Of vital importance is the presence of a largely behind the scenes staff member who takes major responsibility for making it all hap-

pen. Ms. Carol Davis oversees the functioning of my office and all related events, while at the same time maintaining major staff support for the demanding work of the Ethics Committee, the Ethics Appeals Board, and our involvement with the AMA. She has a special ability to develop and implement planning processes and is an extraordinarily knowledgeable and sensitive resource. The nature of her work is such that she rarely receives public attention or recognition. Yet her contributions are invaluable, and she has won the trust and respect of us all.

Comments about "the best in APA" are a good link to my belief that we have been extremely fortunate in our choice of leaders. Dr. Pardes has been an outstanding President whose knowledge, vision, concern, and effectiveness have had a major impact on our functions and our future. His support of the best science, education, and patient care and his positive involvement with a broad range of professional and consumer advocacy groups, such as the National Alliance for Research on Schizophrenia and the Depressions, has strengthened the Association and the field. Our Speaker, Dr. Gerald Flamm, also has been exemplary. His sensitivity to and knowledge of Assembly moods, directions, and needs, as well as his warmth and caring, have made him especially effective for the Assembly and the Association. It has been a privilege to work with all of our members

this year toward a stronger and more effective APA, and I anticipate an excellent alliance with our next President, Dr. Elissa Benedek, and with our incoming Speaker, Dr. Edward Hanin, and all the other APA members who serve the Association and the field so ably.

Extensive reports on the individual staff departments are available from the Central Office. These attest to the diversity, enormity, and complexity of staff efforts and demonstrate our commitment to strengthening the field and supporting our members and the patients they serve. It is a privilege and pleasure to be Medical Director of such a strong and vital organization.

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Report of the Speaker

Gerald H. Flamm, M.D.

The Assembly is a large, heterogeneous group of representatives that meets twice a year as a whole and twice as area councils. Most of our business is carried out in the area councils, which receive and process information from the representatives of the district branches, minority groups, and Members-in-Training. At plenary sessions issues are either approved, tabled, or referred for further discussion and/or action to the Assembly Executive Committee, Joint Reference Committee, and/or Board of Trustees.

The Assembly officers' attendance at area council meetings has been highly informative in regard to local concerns and has been greeted favorably by the area councils. It has also helped the Assembly carry out its business and most appropriately address the concerns of our members. The attendance has also educated the Speaker and Speaker-Elect about the strengths and expertise of individual representatives, enabling appropriate appointments of Assembly committee members and liaisons to APA components; it has also provided the Speaker-Elect with experts to recommend to the President-Elect for appointment to APA components.

Thanks to the efforts of the officers, area representatives, and deputy representatives, the valuable contributions from minority and Member-in-Training representatives, and the active participation of officers in area council meetings, we have accomplished a great deal and several issues with high priority for deliberation and planning have been identified. The following are the most pressing and have been determined by the economic environment and the need to do more with less.

1. *The aging of members and its impact on dues collection.* With an increase in the number of members who reach Life status by fulfilling the "95" requirement—i.e., their age plus years of membership in APA totals 95—dues income falls while expenses continue to rise. Some district branches suffer and report a need for prompt relief. Since the problem has been clearly recognized, several plans are under consideration and a committee has been appointed to make recommendations on alternatives.

2. *Managed care.* This approach has become increasingly promi-

nent in medical care. While quality is given lip service, some agencies have addressed "the bottom line" at the expense of adequate patient care and treatment. The APA Central Office is collecting examples of abusive practices, and a component has been appointed to address the issues involved. Several model statutes aimed at making reviewing agencies accountable for their actions have been introduced into state legislatures, and additional strategies are being considered. Please report examples of abuses to the APA Office of Economic Affairs.

3. *Practice parameters.* The federal government has begun to develop parameters for practice by all physicians. APA, in cooperation with the AMA and other specialty societies, has begun projects in the field. A principal goal is to maintain a clinical focus that will address availability, adequacy, appropriateness, and outcome of care and will demonstrate that what we do warrants the expense and probably reduces overall longer-term general health care costs. Literature review and the application of clinical experience will be brought together in a process that will extend over a number of years. Clinicians, researchers, and, probably, patient groups will be involved over time. A component to review suggestions and define goals and methods will be appointed soon for preliminary work.

I have been giving a great deal of thought to questions about the election process. About 40%–45% of APA members vote. Who does and does not vote, and why? How do voters choose for whom they vote? Is it name recognition, i.e., publications and lectures? Is it statements in *Psychiatric News*? Does receiving letters of support from members you know influence how you vote? Does geographic base significantly determine for whom members vote? Is the membership satisfied with the present system, and are there suggestions for how to improve it? Despite the deficiencies, we have been fortunate to have had good candidates; even though losing candidates have been hurt, the organization has not.

About 41.9% of the eligible members voted in this year's election. While this is not too bad a turnout for a large membership organi-

zation, I would like to see more membership voting, as one index of interest in APA and our efforts on their behalf.

My recent predecessors addressed the composition of the Assembly with creativity and scholarship. Progress has been made, reducing the urgency noted in the past. The Assembly Committee on Planning continues its work on representation, caucuses, and affiliation with external organizations and specialty groups. I want to reemphasize the critical differences between representation in governance, liaison and communication, and subspecialization. The Ad Hoc Committee on Subspecialization, Dr. James Trench, chairperson, has developed guidelines, which have been approved. They will be applied to groups seeking such status. Geriatric psychiatry has been approved as warranting consideration for "added qualifications," and the application is now in the hands of the American Board of Psychiatry and Neurology. Several other groups have indicated an interest in such recognition of their subspecialties, e.g., alcohol and drug abuse (addiction), consultation-liaison, and forensic psychiatry. Others will undoubtedly emerge. This issue is not directly related to governance.

The Committee on Alcoholism and the Committee on Drug Abuse of the Council on Psychiatric Services have been terminated, and the Council on Addiction Psychiatry has been added to the governance structure.

Many external organizations have indicated interest in affiliating with APA in different fashions. Some have requested assistance with lobbying efforts; others would like representation on or affiliation with related councils or committees; still others would like more opportunity to be heard without having a vote.

I strongly endorse receiving as much input as possible from organizations and individuals and encourage oral and written communications to district branches, Assembly officers and representatives, committee chairpersons and members, and APA officers and staff. An example of membership impact through communication was the effective campaign to change the date of the scheduled meeting with the German Society of Psychiatry and Nervous Diseases.

Dr. Paul Fink, a past President, has been meeting with external organizations and has mobilized interest in affiliation with APA, which has led to closer relationships. Ultimately, these affiliations may lead to direct representation of those organizations in APA. The role of the Assembly and its structure are topics of ongoing discussion by the Committee on Planning.

Unfortunately, despite coverage in *Psychiatric News*, district branch newsletters, and reports from the Joint Commission on Government Relations, the Joint Commission on Public Affairs, and the Division of Economic Affairs, many members do not feel adequately informed; continued education is necessary. The forums for the district branch presidents-elect and staffs before the 1989 fall Assembly meetings involved more members than ever before and, together with the stimulating orientation of the district branch presidents-elect, executive secretaries, and directors, provided another level of education and communication.

As I complete my term as Speaker, I want to thank the Assembly for permitting me to serve. It has been a rewarding and satisfying experience for me, and a great deal has been accomplished by the Assembly. It has matured, gained respect, and grown in stature. Solid working relationships have been established with the Board of Trustees and the Joint Reference Committee. The Assembly has participated in the bridging of components and has increased input from and transmission to the membership at large.

I have been fortunate to have worked with such outstanding people. Dr. Melvin Sabshin, our Medical Director, is a remarkable leader and executive. His national and international activities and standing are beyond words. He has developed an extremely impressive staff and very early recognized Dr. Carolyn Robinowitz's ability and helped her develop into his sound and reliable backup. She, like Dr. Sabshin, has been a valuable facilitator of Assembly and APA business. The other deputy medical directors and the directors of the staff offices have been supportive and highly cooperative and have often sought the advice and reaction of the Assembly.

Ms. Claudia Hart's work with the Joint Reference Committee and in developing the joint meetings of the Joint Reference Committee and the Assembly Executive Committee was of notable assistance and is warmly acknowledged. I deeply appreciate both the value and style of Ms. Lea Mesner and Ms. Jeanne Robb in their work with the Board of Trustees and support of the Assembly. Jeanne Robb is the spirit, historical memory, organizer, and backbone of the Assembly. Despite her recent adversity, she carried on with tireless efficiency. Thanks to Mr. Michael Murphy's ability to learn quickly, he has been reliably available to assist Jeanne and the Assembly.

One additional special pleasure I have had is working with our President, Dr. Herbert Pardes. He is more of a Renaissance man than anyone I know—teacher, researcher, clinician, administrator, and brilliant leader who listens, quickly understands, focuses, and cuts Gordian knots with ease. He has been inspirational and has increased the public's and our understanding of how research translates into clinical practice and good patient care.

My job would not have been possible without the invaluable assistance, support, and friendship of our Speaker-Elect, Dr. Edward Hanin, and Parliamentarian, Dr. James Trench. Ed's contributions have been crucial in numerous committees, and the Assembly's reputation has been enriched by them. Our past Speaker, Dr. John McIntyre, and Recorder, Dr. Bernice Elkin, were available whenever I needed them, and I appreciate their help.

Not to be overlooked, the area representatives and their deputies and the minority and Member-in-Training representatives and their deputies deserve my profound thanks for their hard work in the areas and their generous contributions to all of us. And finally, each and every member of the Assembly has played a role in advancing the business of the body and its reputation, and I express my appreciation for their cooperation and support.

Report of the Speaker-Elect

Edward Hanin, M.D.

My year as Speaker-Elect was truly an incredible learning experience. That is really what an "elect" year should be, an opportunity to learn from others how to do it right before one carries the full burden of office. I cannot say what kind of student I have been, but I can tell you that I have had some pretty wonderful teachers.

The Speaker-Elect serves as vice-chairperson of the Joint Refer-

ence Committee, is invited to attend meetings of the Budget Committee, and sits on the Board of Trustees, with voice. In addition, during the past year, I was privileged to serve on the Board Committee on Insurance, the Ad Hoc Committee to Evaluate Quality Assurance Activities, and the Ad Hoc Committee on Managed Care. In all of these assignments I was the Assembly's representative, and

I hope that I was able to fairly and accurately present the sense of the Assembly. I was exposed to a broad range of issues and had an opportunity to hear both from APA leadership and from the members in the district branches.

As I have represented the Assembly in a number of different arenas, I have felt proud of the respect in which the Assembly is held throughout our organization. That the Speaker of the Assembly sits next to the President at Board meetings is not empty symbolism. It represents the importance of the deliberations and actions of the Assembly, not only to us within that body, but to others at all levels of APA activity. There is no meeting I attend where, as an issue is being debated, someone does not turn to me and ask, "How will the Assembly feel about this?" or "What would the Assembly want to see happen here?" The Assembly is seen as a valuable conduit for the ideas of the members, the psychiatrists in the district branches who practice in the wide variety of modes and settings that represent the strength of this profession. The deliberations in the area councils and the debates on the floor of the Assembly have increasingly shown a responsible participation in the framing of approaches and solutions to the many issues presented to us. Many APA committees, especially those developed to deal with emerging issues, are more likely than not to be joint Board-Assembly committees with members appointed by both President and Speaker.

Particularly gratifying to me has been the growth of the role of the Assembly Executive Committee, both in acting for the Assembly between meetings and in developing strategies to effect the actions taken by the Assembly, since such a role was first proposed by the Assembly Committee on Planning. I do not think any of us foresaw what an effective body it would become in just a few years. All this did not just happen. It is the result of the tremendous leadership our past Speakers have given to the Assembly. I would especially like to note the ones with whom I have worked most closely: Drs. Roger Peele, Irvin Cohen, and John McIntyre. Their breadth of vision, their ability to shape debate so that, although meaningful and intense, it never became acrimonious, and the tremendous respect they engender in all with whom they work have had much to do with making the Assembly the vital body it is today.

Dr. Gerald Flamm, our Speaker, is a delight. I am introduced to more people when I walk down a corridor with Gerry than in all my prior years in APA. He knows everyone, likes everyone, and is well liked by them. His devotion to the Assembly and to APA is incredible, and the sacrifices he has made on our behalf are known only to those who know how hard he works to represent our views. He listens carefully, always considers how practitioners would be affected, and once having made his decision, is a forceful and fluent advocate. Watching him operate, and I mean that in the best sense of the word, is to understand what is meant by leadership. I have tried to take notes, especially on all his jokes, but I doubt that I will be able to tell them nearly as well as the master.

The Joint Reference Committee is a relatively new body in the APA governance structure and, as such, is still undergoing change and development. It provides an opportunity for council chairpersons, Assembly officers, and representatives from the Board to together digest and focus issues for final decision by the Board of Trustees. This year the Joint Reference Committee was ably chaired by Dr. Elissa Benedek, our President-Elect. She is an incredibly skilled chairperson. The Joint Reference Committee is a large group, the issues are complex, and members' opinions differ, sometimes strongly. Dr. Benedek's ability to allow a free and full discussion while getting a diverse group to collaborate and proceed through an agenda is a true gift. This was the second year that a joint meeting of the Joint Reference Committee and Assembly Executive Committee was held. Unlike the somewhat ceremonial first meeting, this time the two groups were given two of the toughest items on the APA agenda, managed care and practice parameters. The discussion was freewheeling and intense. Neither group felt in the least constrained or intimidated by the presence of the other, and the final outcome of the collaborative discussions was better than either group could have achieved on its own. It served as a model of how Board-Assembly collaboration can effectively direct APA toward creative solutions for difficult problems.

The President-Elect and the Speaker-Elect spend a lot of time together working on appointments. Dr. Benedek has been extremely

sensitive to the value of Assembly input in the appointment process. Since many more of our dedicated members offer to contribute their time to APA than we are able to appoint to components, I wish I could say that I have nothing to do with appointments. That would simply be untrue. I have been asked for input on every appointment Dr. Benedek has made, and I am most appreciative of her collaboration with me and, really, with the Assembly. I only wish that we could have appointed all the excellent physicians who are willing to work for APA. Dr. Benedek will be a wonderful President and spokesperson for APA. I look forward to her presidential year with great enthusiasm.

My opportunity during the past year to attend meetings of the area councils has given me an even greater appreciation of the caliber and accomplishments of our Assembly members and of the area officers. Each area is unique, but all share a determination to think through the critical issues facing psychiatry today. The quality of the discussions is truly impressive. Area councils are a valuable and, I think, underutilized resource of APA. They are close to the grassroots of the organization, having representatives from every district branch, Members-in-Training, and the minority and underrepresented groups as well.

The legislative and public affairs networks often meet at the time of the area council meeting. We need to look at ways in which the area councils can be better used to convey information to our members and to bring member input to our leadership.

We have a wealth of talent in the Assembly. Our members show their worth and dedication not just in the debates on the floor at Assembly meetings, but also in the way they participate in their councils. I will certainly be looking to the Assembly for lots of help in the next year.

APA has wisely placed responsibility for the oversight of government affairs and public affairs in the hands of joint commissions, bodies responsible to both the Board and the Assembly. Members of these commissions are selected by area councils and meet with their respective area councils. The chairpersons report directly to the Assembly. APA's activities in these two areas are critical to the success of any efforts to overcome stigma, educate the public and government, and advance legislation in the interest of our patients and members. Through networks they link all the district branches. The public affairs and legislative representatives of the district branches work hard and are becoming increasingly important, as so much legislative and regulatory activity is shifting to the local level. This past winter I attended the excellent State Legislative Institute at Dana Point, Calif., organized by the Joint Commission on Government Relations and the Division of Government Relations. In February 1991, a public affairs institute will be held for the district branch public affairs representatives. I look forward to attending, and I know from past experience it will be a valuable experience for me and for all who attend.

APA has been most fortunate to have Dr. Herbert Pardes as our President this past year. His ability to organize, to synthesize, and to reach decisions quickly has been especially important during these fast-moving times. He is a skilled, articulate spokesman for psychiatry and psychiatric patients. He has worked hard to forge links with advocacy groups, whose support of psychiatric research has been a vital element in obtaining increased funding for research. He has been a true statesman and leader.

No report of a Speaker-Elect can be complete without much praise and thanks to the Central Office staff. Dr. Melvin Sabshin and Dr. Carolyn Robinowitz have been both most supportive of me and very patient as I have proceeded with my on-the-job training. We are very fortunate to have such physicians working for our patients and our profession. We need such individuals as our advocates. The past year, in many ways, has not been an easy one for the APA Central Office. The skill with which difficult decisions were made and difficult actions carried out by Mel Sabshin, ably assisted by Carolyn Robinowitz, will allow APA to continue to be a strong and effective operation.

I have learned to have tremendous respect for Mr. Jay Cutler and the staff of the Division of Government Affairs and the Office of Economic Affairs. Equally, Mr. John Blamphin and the staff of the Division of Public Affairs deserve praise for their efforts on our behalf.

Ms. Claudia Hart's work with the Joint Reference Committee deserves special mention, as do the efforts of Ms. Lea Mesner with the Board, Mr. Michael Murphy with the Assembly, and Ms. Alison Bondurant, who was of great help to Dr. Benedek and me in the appointment process. Mr. George Campbell, Ms. Olga Damschen, and the staff of the Office of Meetings Management have been most helpful and creative in ensuring that the meetings of the Assembly and its committees run smoothly.

Ms. Jeanne Robb deserves very special thanks from all of us. She makes everyone she works with look good. If I have done things well, it was because I followed her advice. If things turned out bad, it was because I did not. She has been of invaluable assistance to me. She is a remarkable human being and a true friend. Jeanne, thank you.

A number of critical issues will require close attention from the Assembly and, indeed, from the entire organization during the next year. Let me mention those I feel will require special efforts.

Managed care means many different things to different people. However, we all know that whatever it is, we are living with it and will be for the foreseeable future. It has had and will continue to have an impact on the economic environment in which we practice. Whether as a physician working for a health maintenance organization or preferred provider organization or as a private practitioner pleading with nonmedical utilization review personnel for a few more days to allow a patient's condition to stabilize or a few more visits to consolidate gains made, many of us are practicing in ways quite different from those with which we were familiar. Managed care has not arisen in a vacuum. It is an attempt by government, insurance companies, and employers to control costs, which are felt to be too high. Unfortunately, as an industry it has developed very rapidly, has few if any standards, is unregulated, and can create havoc when it attempts to achieve cost savings at the expense of quality care. APA's response must be multifaceted. Clearly, members need help in coping with the flood of calls from reviewers, many of whom seem to know very little about psychiatric illness. There is a need to educate the public about the limitations of certain coverage, limitations of which they are often unaware. We need to determine whether the alleged increases in the cost of treating psychiatric illnesses truly exist and, if so, what we can do about them and, if not, how to disseminate this information. We need to educate our members about the economic realities of health care as they emerge and prepare members to practice in the new treatment settings in an ethical and professional manner. We need to be alert to the movement toward some form of national health planning and be prepared to shape the proposals in ways beneficial to our patients. The Ad Hoc Committee on Managed Care has come up with a plan for action, approved by the Board of Trustees, which will help launch such activity.

On the basis of the Assembly's recommendation for the formation of a permanent component on managed care under the Council of Economic Affairs, such a committee was approved by the Board and now has its charge and should soon become active. This committee will need to determine longer-range strategies for effectively collaborating with the providers of health care coverage and for establishing reasonable standards for utilization review and reviewers. APA will be making a major commitment of resources to these activities, but we must. Our members have indicated their feeling that this is the single most important issue affecting their practices, and we must do something to help. This will clearly be a major area of discussion and interest in the Assembly.

Members expect APA to be aggressive in pursuing the interests of psychiatry. They expect us to be proactive, not reactive, and on top of crises, not under them. They want APA to battle hard on behalf of the mentally ill. To my mind, APA has done incredibly well in this regard, but there are always new challenges. For example, APA's activity on behalf of members in the areas of managed care and practice parameters is vital but costly. Yet member dues cannot rise beyond reason, and alternative sources of revenue are not obvious. Some say APA should prioritize and decide which of all the good things it does are most essential. But who is willing to see their special area of interest receive a low priority? The joint Board-Assembly Ad Hoc Committee on Membership and Fiscal Policies is studying the whole issue of member dues and member satisfaction.

After our remarkable success in attracting Members-in-Training, there are not many left to bring to APA. We will probably not see the kind of growth in membership that was seen in the 1980s, and like the country in general, we will be aging as an organization. We are already seeing a loss of members from district branches with high dues. Yet these district branches, like the national organization, are asked to be more and more active while still receiving only dues as revenue. Some recommendations from this ad hoc committee will be heard at the next Assembly meeting. They will need to be carefully reviewed. However, the work of this task force will be ongoing, and I see further recommendations for action as another substantial issue for the Assembly during the next year.

At this annual meeting, the Assembly will be reviewing the criteria for subspecialty status. The trend is obvious, and we already see a myriad of special psychiatric organizations emerging. Some represent practice specialties, and others focus on practice settings (private practice, the military, community mental health centers, etc.). Yet others reflect the background or country of origin of the membership. Such diversity is healthy and invigorating so long as it does not fragment APA or, even more important, the profession of psychiatry. Dr. Paul Fink should be commended for focusing our attention on fragmentation during his presidential year. A dozen voices, all claiming to speak for American psychiatry, do not have the clout of a single voice that represents all of psychiatry. Yet such unanimity comes about only if all psychiatrists truly feel part of APA and fully represented. APA has been described as a tent in which all of the various special interests can be comfortable. But how do we ensure that members continue to feel at home in APA, that their interests are truly understood, and that they would not be better served through membership in some other, more narrowly focused organization? As costs rise and our members' incomes do not keep pace, this will be an increasingly important factor. A lot of good thinking has gone on so far, but to my mind, we have not come up with good solutions. The character of the Assembly, and whether it can continue to develop and change as a representative body, appears to me to be critical to the outcome.

We in psychiatry are facing so many issues critical to our specialty that I am almost embarrassed to suggest that APA governance and structure is something on which we need to spend time. But it is. Our ability to react quickly and implement solutions quickly is key to our success as an organization, no matter what the substantive issue. I have seen the increased use of ad hoc task forces, often appointed jointly by the Board and Assembly, as a way of quickly bringing together an action-oriented group that can present recommendations to the Board.

This mechanism has served us well in several areas, but it does ignore the existing council and component structure. It requires the Board to too often act as a committee of the whole, without the usual predigestion of issues our component structure and Joint Reference Committee should provide. I am personally delighted at the way in which the Assembly Executive Committee has been able to act between meetings of the Assembly to provide meaningful Assembly input into the deliberations of other elements in the organization. I have seen the Assembly grow in significance as a result of this and become more careful and responsible in its deliberations and recommendations. However, the Assembly Executive Committee is not the Assembly, and we must be careful not to substitute the workings of a small dedicated group for the deliberations of the larger body. I will try, through my appointments, to make sure the Assembly membership is included as much as possible in the deliberations on critical issues and to be sure such discussions are brought early to the attention of the Assembly.

I have saved for last what I feel may be the most important and difficult issue facing us today: the development of meaningful and usable practice standards for the field. These parameters are likely to define the practice of psychiatry for the foreseeable future. If these are not formulated carefully and well, we will have done the field a grave disservice. If we do not formulate them at all, others will do so for us, with grave consequences for our patients. Our standards must be developed as part of the effort by all of medicine, but no one but psychiatry can define our practice standards. I was pleased with the discussion in the joint meeting of the Assembly Executive Committee and the Joint Reference Committee on parameters of care and with

their recommendation that a special Board-Assembly committee be established to begin work on such parameters. This committee will have to consult many components of the organization, draw on the expertise of distinguished researchers and educators, and ensure a sound research base. To me, the most critical element in the development of these standards will be the input of clinically experienced practitioners. Such input will be critical to their quality, their usefulness, and their acceptance by psychiatrists who directly treat patients. I feel this is the major task for our profession at this time and feel confident that it will be done well. We are not starting from ground zero. The widely admired *Treatments of Psychiatric Disorders* (1) and our task force report on ECT (2) provide a foundation that will make the task somewhat easier.

I am sure that I have forgotten to express my appreciation to many people who have made this year an exciting and stimulating one for me, e.g., my colleagues on the Assembly Executive Committee and the Joint Reference Committee, the Assembly members I have met and worked with. If I have forgotten anyone, it is because of my poor memory, not any lack of appreciation. I have had a tremendous role model in our current Speaker. Although I do not expect to match his accomplishments, I do look forward to a challenging and productive year. The ability of all of us—Board, Assembly, councils, committees, district branches, staff, and, most important, our members—to work together and see ourselves as a single effective force will help keep psychiatry the dynamic and creative profession it has always been.

REFERENCES

1. Karasu TB (ed): Treatments of Psychiatric Disorders: A Task Force Report of the American Psychiatric Association. Washington, DC, APA, 1989
2. American Psychiatric Association Task Force Report 14: Electroconvulsive Therapy. Washington, DC, APA, 1978

Report of the Committee on Constitution and Bylaws

Ralph A. O'Connell, M.D., Chairperson

The Committee on Constitution and Bylaws held one formal meeting this year. I wish to thank the members of the committee, Drs. Henry Payson, Gerald Sarwer-Foner, Walter Shervington, William Spriegel, and Richard Thurrell; our Assembly liaison, Dr. Lee Park; and staff member Ms. Carol Lehmann for handling committee business expeditiously.

The committee discussed several issues that were referred to it by the Board of Trustees and originated in the Committee on Membership. It prepared amendments that, if passed, would 1) extend the option of Corresponding Membership to psychiatrists living in Mexico, Central America, and the Caribbean, 2) exempt medical students from the dual membership requirement and yearly dues, requiring only a one-time fee when they join, and 3) abolish the category of Associate Membership but allow members currently holding this status to retain it.

The Board approved all amendments for reading to the membership at the 1990 annual meeting and placement on the 1991 ballot. The text of the amendments follows.

Proposed Amendments to the Bylaws

The following amendments were approved by the Board of Trustees in December 1989 and March 1990 for reading to the membership at the 1990 annual meeting. The amendments will be disseminated to the membership not later than Jan. 1, 1991, and will appear on the 1991 ballot. In the text below, brackets indicate deletions and italics indicate additions.

Proposed amendment 1. This change would extend the option of Corresponding Membership to members permanently residing in Mexico, Central America, and the Caribbean.

Chapter One. Members

12. Corresponding Fellows and Members shall be physicians living outside the jurisdiction of the Association who would otherwise be qualified for membership. *Physicians permanently residing outside the jurisdiction of a District Branch but within the jurisdiction of the Association who would otherwise be qualified for membership may become Corresponding Fellows and Members.*

Proposed amendment 2. This series of amendments would exempt medical students from the dual membership requirement and yearly dues, requiring only a one-time fee when they join.

Chapter One. Members

4. (a) Medical Student Members shall be physicians-in-training who are enrolled in a school of medicine, including schools of osteopathic medicine. Medical Student Membership shall not include voting privileges, *nor shall years as a Medical Student Member count toward eligibility for Life Membership or Life Fellowship.*

Chapter Two. Membership Processing

1. Admission to membership *(other than Medical Student Members)* shall require valid election by the appropriate District Branch approved to process membership applications, with certification by the Membership Committee that constitutional requirements have been met. *District Branch membership is waived for Medical Student Members until graduation from medical school, at which time those Medical Student Members eligible for Member-in-Training status must join the appropriate District Branch in order to advance to Member-in-Training.*

An applicant for membership may be refused election or promotion to more advanced membership, or transfer to another District Branch, on the basis of the provisions of Chapter One of the Bylaws or on the basis of criteria of ethical and professional suitability established by the Board and the Membership Committee and applied by the appropriate District Branch. A rejected applicant must be informed by the District Branch of the right to appeal through the Recorder to the Assembly for adjudication.

If the local District Branch is not approved by the Board to process membership applications the District Branch shall for-

ward the application with its recommendation to the Membership Committee of the Association.

An applicant for membership who does not live or practice within the jurisdiction of a District Branch, *or an applicant for Medical Student Membership*, may apply through the Secretary of the Association.

The Board shall be the final judge of the acceptability of all candidates for membership.

2. Advancement to Member-in-Training from Medical Student Member *shall require valid election by the appropriate District Branch*. [and] *Advancement* to General Member from Member-in-Training or Associate Member shall be by the same process as for election to membership.

Chapter Eight. Privileges and Responsibilities

6. Every Fellow, General Member, Associate Member, *and* Member-in-Training [and Medical Student Member] shall pay both dues and assessments as determined by the Board and the District Branches. *Medical Student Members shall pay a one-time, national membership dues.* All other categories of membership shall be exempt from paying dues and assessments to both the Association and its District Branches. A dues-paying member shall be exempt from paying such dues and assessments when the sum of the member's years of active membership in the Association plus the member's age at the start of the fiscal year shall equal 95.

Such dues will include amounts allocated to subscriptions for *The American Journal of Psychiatry* and for *Psychiatric News*.

The membership application shall contain a provision for allocation of a specific portion of the dues to pay the cost of periodical subscriptions to these publications. Dues exempt members shall pay a reduced subscription rate for these publications if such members desire to receive them.

Proposed amendment 3. These amendments would abolish the category of Associate Membership. Members currently holding this status would be permitted to retain it, but no new applicants would be accepted.

Chapter One. Members

4. (b) Members-in-Training shall be physicians who have been accepted into an approved psychiatric residency training program. Member-in-Training status shall not exceed six years, and upon completion of approved residency training, Members-in-Training shall be advanced to General Membership. [If approved residency training is not completed within six years, Members-in-Training shall be transferred to Associate Membership.]

5. Associate Members shall be physicians who have completed at least one year of acceptable full-time training or experience in psychiatry, *and who have been granted Associate Membership status by December 1989*, but are not eligible for Member-in-Training or General Membership categories. Associate Members must either have a valid license to practice medicine or hold an academic, research, or governmental position that does not require licensure.

Report of the Committee on Membership

Michael J. Vergare, M.D., Chairperson

The Committee on Membership met on Sept. 12, 1989, and Nov. 7–10, 1989, in Washington, D.C. Present were Drs. Michael J. Vergare (chairperson), Jack W. Bonner III, Fernando J. Cabrera, Lois B. Fuller, Robert L. Leon, Rodrigo A. Munoz, Donna M. Norris, Norman Rosenzweig, Aron S. Wolf (Assembly liaison), John S. McIntyre (consultant), Siobhan Coomaraswamy (consultant), Marta DeLalla (Director, Office of Membership), and Office of Membership staff. The following guests were also present: Drs. Melvin Sabshin (Medical Director), Carolyn B. Robinowitz (Deputy Medical Director), Nada Stotland (chairperson, Committee on Women), Steven Sharfstein (chairperson, Budget Committee), Ronald Shellow (chairperson, Assembly Committee on Planning), David J.M. Whitehouse (chairperson, Committee of Young Psychiatrists), Robert McDevitt (chairperson, Ethics Committee), and Captane Thomson (President, California Psychiatric Association) and Ms. Andrea Morgan (Director, Office of Resource Development). The committee met jointly with the Assembly Committee on Recruitment/Retention and Membership Affairs on Friday, Nov. 10, 1989.

INFORMATION ITEMS

Membership Development

The total membership as of April 1, 1990, was 36,348. The APA membership increased from 25,345 members in January 1980 to 36,208 at the beginning of 1990, for an average net gain of over

1,080 members per year. The distribution by member class in each year since 1984 can be seen in table 1.

The committee reviewed the extensive recruitment activities of the Office of Membership. Recruitment projects included, but were not limited to, contacting residency training directors and chairpersons of departments of psychiatry for their assistance in recruitment of residents and medical students, working with the Office of Research in recruiting research psychiatrists, and contacting 725 psychiatry residents in postgraduate year 1 (as reported in the 1988 resident census) and diplomates of the American Board of Psychiatry and Neurology and inviting them to become members.

The value of retaining younger members continues to be evident. During 1989, 1,070 Members-in-Training were advanced to General Membership, compared with 922 during 1988. Table 2 shows the numbers of General Members gained through enrollment and through advancement from Member-in-Training for the past 5 years.

Overall, the numbers of enrollments and reinstatements were higher in 1989 than in 1988. Membership transactions during all of 1989 can be seen in table 3.

Committee of Young Psychiatrists

The Committee on Membership met with David J.M. Whitehouse, M.D., chairperson of the Committee of Young Psychiatrists, and discussed mutual concerns regarding issues confronting those just starting their careers in psychiatry. One topic was graduated APA dues, which would ease the transition from Member-in-Train-

TABLE 1. Members in Each Class, 1984 to 1990

Membership Class	Jan. 1, 1984		Jan. 1, 1985		Jan. 1, 1986		Jan. 1, 1987		Jan. 1, 1988		Jan. 1, 1989		Jan. 1, 1990	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Medical Student Member	0	0.0	208	0.7	420	1.3	605	1.8	608	1.8	658	1.9	721	2.0
Member-in-Training	3,310	11.4	4,220	13.8	4,485	14.1	5,054	15.1	5,366	15.6	5,594	15.9	5,856	16.2
Associate Member	322	1.1	326	1.1	334	1.0	330	1.0	302	0.9	263	0.8	228	0.6
General Member	17,170	59.2	17,195	56.4	18,135	57.0	18,340	54.9	18,653	54.4	18,847	53.6	19,299	53.3
Fellow	3,736	12.9	3,628	11.9	3,497	11.0	3,758	11.3	3,770	11.0	3,546	10.1	3,534	9.8
Life Member	980	3.4	1,107	3.6	1,070	3.4	1,231	3.7	1,365	4.0	1,700	4.8	1,844	5.1
Life Fellow	2,308	8.0	2,518	8.3	2,566	8.1	2,609	7.8	2,753	8.0	3,033	8.6	3,133	8.7
Life Associate	29	0.1	28	0.1	30	0.1	34	0.1	39	0.1	52	0.2	55	0.2
Inactive Member	502	1.7	580	1.9	601	1.9	587	1.8	682	2.0	713	2.0	745	2.1
Inactive Fellow	139	0.5	145	0.5	137	0.4	129	0.4	132	0.4	119	0.3	115	0.3
Corresponding Member	247	0.9	284	0.9	292	0.9	334	1.0	350	1.0	362	1.0	393	1.1
Corresponding Fellow	205	0.7	211	0.7	208	0.7	219	0.6	222	0.6	220	0.6	228	0.6
Distinguished Fellow	29	0.1	29	0.1	29	0.1	30	0.1	30	0.1	30	0.1	28	0.1
Honorary Fellow	32	0.1	35	0.1	33	0.1	33	0.1	34	0.1	31	0.1	29	0.1
Total	29,009	100.0	30,514	100.0	31,837	100.0	33,293	100.0	34,306	100.0	35,168	100.0	36,208	100.0

TABLE 2. General Members Gained From Enrollment and Advancement, 1985 to 1989

Year	Total New General Members	Enrolled	Advanced From Member-in-Training	
			N	%
1985	1,121	480	641	57
1986	1,107	395	712	64
1987	1,105	285	820	74
1988	1,185	263	922	78
1989	1,285	215	1,070	83

ing dues to first-year General Member rates. The difference between these rates in 1990 is $155 ($70 and $225), and of the 63 district branches using the centralized billing service, only five have graduated dues for General Members. The Committee of Young Psychiatrists recommended that all district branches consider graduated dues to allow a smoother transition, and the Committee on Membership endorsed that recommendation.

Concern was expressed over the fact that some district branches bill at the General Member rate before formal advancement from Member-in-Training, and it was recommended that this practice be discontinued.

The committee defines "young psychiatrists" as those under age 40 and/or within the first 5 years of practice after training. To help young psychiatrists make the transition from residency to practice and to minimize the potential for fragmention, the Committee of Young Psychiatrists recommended, and the Committee on Membership endorsed, the establishment of committees of young psychiatrists at the district branch level.

Dr. Whitehouse reported that his committee is working toward the establishment of a resource book addressing supervision, confidentiality, peer review, setting up a private practice, ethics, and career development. Such a publication would be of value to psychiatrists who are moving from training to their psychiatry careers. The committee reviewed what the Office of Membership sends in its packet for new members, with a view toward expanding it to include more of the information the Committee of Young Psychiatrists was considering developing.

Medical Student Members

Fifty-five district branches responded to a questionnaire concerning proposed changes to the policy governing membership for medical students. An overwhelming majority of the respondents were in favor of the following changes: 1) a one-time fee for national dues, as opposed to annual dues, and a waiver for Medical Student Mem-

bers who have already paid dues, and 2) exemption of Medical Student Members from the APA/district branch dual membership requirement, allowing APA affiliation only. All branches will be provided with lists of Medical Student Members in their jurisdictions to facilitate interaction and communication. A proposal to make these changes to the Constitution and Bylaws will be placed on the 1991 ballot.

Committee on Women

During its meeting in September 1989, the Committee on Membership welcomed Dr. Nada Stotland, chairperson of the Committee on Women, and discussed issues and APA activities of importance to female psychiatrists.

Dr. Stotland advocated increased collaboration between the two committees to enhance the recruitment of women into APA and to devise means of better serving their needs and interests. Specifically, Dr. Stotland requested that the Committee on Membership support the Committee on Women in its efforts to obtain direct funding from APA for the Committee on Women Activity Center at the annual meeting (making it a line item), rather than having to rely on the vagaries of outside funding; the cost of these activities is estimated at $8,000 per year. The Committee on Membership recognizes that this center is an important gathering place where information about the Association is exchanged, and it encourages funding for this activity. Staff from the Office of Membership will lend support to the center during the annual meeting to the extent that their other responsibilities permit.

Dr. Stotland discussed means to ensure that female psychiatrists are well integrated into the governance structure, particularly at the district branch level, and suggested enhanced interaction between the district branches' membership committees and committees on women. Dr. Stotland indicated it is also necessary to recognize that women must often assume multiple roles and that financial hardship may result from family obligations and consequent reductions in professional activities; therefore, flexibility must be demonstrated with respect to requests for dues relief.

Some of the other issues discussed were the impact of subspecialization on women (both as patients and physicians), the disparity in the proportions of men and women certified in psychiatry, and the impact on women of the proposals for recertification.

Census of Residents

Detailed statistical information compiled from the 1988–1989 APA census of residents was distributed. A total of 6,048 residents were reported for the 1988–1989 census year. The committee noted that there was a sizable increase in the number of physicians undertaking psychiatry residency training (an increase of 219 over the 1987–1988 census year). The number and percentage of female res-

TABLE 3. 1989 Membership Transactions

Transaction[a]	Number
Gains	2,042
New members	1,930
Medical Student Members	316
Members-in-Training	1,357
General Members	215
Members-at-Large	4
Corresponding Members	29
Corresponding Fellows	8
Honorary Fellows	1
Reinstatements	112
Medical Student Members	1
Members-in-Training	23
General Members	86
Fellows	1
Inactive Members	1
Losses	1,002
Resignations and drops	787
Resignations from APA	211
Drops for nonpayment of APA dues	412
Drops/resignations from district branches and thus from APA	164
Verified deaths	215
Net gain	1,040
Changes in membership status	1,906
To Member-in-Training from	176
Associate Member	1
General Member	27
Medical Student Member	148
To General Member from	1,075
Medical Student Member	1
Member-in-Training	1,070
Inactive Member	2
Associate Member	1
Corresponding Member	1
To Corresponding Member from General Member	5
To Corresponding Fellow from Corresponding Member	3
To Fellow from	207
General Member	204
Life Member (to Life Fellow)	3
To Life status from	440
Fellow (to Life Fellow)	180
General Member (to Life Member)	186
Life Member/Fellow (to 50-Year Life Member)	69
Associate Member (to Life Associate)	5
Transfers of district branch affiliation	1,158
Between district branches	1,103
From Member-at-Large to a district branch	32
From a district branch to Member-at-Large	23
Recommendations for deferral or denial of Fellowship status	37
Deferral of transfer of General Member to Fellow	35
Denial of waiver of 2-year waiting period for renomination for Fellowship (not reviewed)	1
Denial of waiver of 8-year General Membership requirement for Fellowship (not reviewed)	1
Requests for dues relief or Inactive status	318
Approved	265
Dues waivers	115
Dues waivers for reinstatement	5
Dues waivers to reach Life status	45
Reduction of dues	24
Refund of dues	3
Extension/deferral of payment	2
Transfer to Temporary Inactive status	9
Transfer to Permanent Inactive status	62
Deferred or denied	53
Temporary Inactive status	1
Permanent Inactive status	4

TABLE 3. (continued)

Transaction[a]	Number
Deferred or denied, cont'd	
Dues waivers	23
Reduction of dues	6
Refund of dues	1
No action pending district branch recommendation	18

[a]In addition, 7,595 address changes were processed. This number may be underinclusive since it reflects only one change per member and multiple changes are not reported.

idents continue to increase as well: 582 more female psychiatry residents were reported in the 1988–1989 census than in 1984–1985, compared to an increase of 154 male residents. The statistical data were sent in September 1989 to all directors of psychiatry residency training programs and chairpersons of departments of psychiatry.

Eligibility of 50-Year Members/Fellows for Recognition

In 1969 the Board of Trustees decided that certificates should be presented to fellows and members who have belonged to APA for 50 years and that these individuals should be invited to the Convocation of Fellows and listed in the convocation program at the annual meeting. Since that time, Life Members, Life Associate Members, and Life Fellows (excluding those with Inactive status) have been so honored when they have belonged to the Association for 50 years.

The committee reviewed the question of whether members/fellows with Inactive status who have belonged to the Association for 50 years should be so honored. It was the committee's consensus that the 50-year award should remain as is—only those with 50 years of active membership will be honored as 50-Year Members/Fellows.

Proposal for "Affiliate" Membership

The Maryland Psychiatric Society submitted for review by the Committee on Membership its proposal for an "Affiliate" category of membership, open to those in contiguous district branches. It would enable the Maryland society to coordinate legislative and peer review efforts. Such members would not vote and would pay dues of $50.00 to cover mailings, newsletters, and the district branch directory.

After lengthy discussion, the committee decided that this type of dual involvement could best be encouraged without resorting to a new membership category. The "Operations Manual of the Board of Trustees" states that a member may not hold membership in more than one district branch, and such a change would require a vote of the membership and could possibly cause confusion among members about the APA/district branch dual membership requirement. It was noted that district branches in other areas of the country handle this type of situation by including interested members from other district branches in their activities, without any formal membership action. These members, in essence, are viewed as "friends" of the adjoining district branches.

Survey of Other Associations Regarding Membership

The Office of Membership conducted a survey of 60 organizations (all but four were medical specialty societies) concerning membership/dues policies. The results from 46 responses (76.7%) are as follows.

Membership dues. APA dues for 1989 were in the upper range, the same as those of two other organizations but significantly lower than those of the two associations with the highest dues ($400 for APA compared to $500 and $520). There was no correlation between size of membership and dues level ($r=0.11$, $p=0.24$).

Dues-exempt status. Only four of the respondents indicated that they had no dues-exempt categories of membership. All others had some type of Life/Emeritus/Honorary status. Most of these catego-

ries were based on a combination of years of membership, age, and level of professional activity. The organizations with the highest dues levels are more likely to have a higher percentage of dues-exempt members (r=0.39, p=0.005).

Dues relief. Two organizations reported having no options for dues relief. The majority offered some type of alternative, such as waiver, deferral of payment, reduction of dues, or Inactive status for financial hardship, illness, or disability. One organization had a relief and disaster fund, and members might qualify as relief recipients.

Grace period for dues payment before termination of membership. The grace period ranged from 3 to 36 months (average, 16 months); 17 organizations reported a grace period of 24 months. A statistically significant negative correlation was found between size of membership and length of grace period (r=−0.33, p=0.01), i.e., larger organizations were more likely to have a shorter grace period.

Local affiliation. Thirty-four of the respondents (73.9%) reported no requirements for any type of local affiliation. Larger organizations were more likely to have this requirement (r=0.41, p=0.003); the same was true for associations with student members (r=0.49, p=0.001).

Student and resident members. Thirteen (28.3%) of the respondents reported having student members, while 35 organizations (76.1%) had a category for resident members. Those that offered membership to residents gave higher ratings to the importance of recruitment efforts (r=0.38, p=0.006).

ACTION ITEMS

Associate Member Category

At its December 1988 meeting the Board of Trustees approved the recommendation that no new members be accepted or transferred into the Associate Member category until further study of this membership category is completed. There seem to be insurmountable obstacles in trying to evaluate the credentials and extent of training in psychiatry of applicants for this category. Once these applicants become members of APA, they have access to almost the full range of services, benefits, and privileges of membership in the Association. It was felt that professionals who are not fully trained in psychiatry can best obtain benefits from the organizations representing their primary specialties, thus protecting the reputability attached to membership in APA.

The Assembly, at its November 1989 meeting, approved the recommendation of the Assembly Committee on Recruitment/Retention and Membership Affairs that this category be abolished, and in December the Board of Trustees approved the recommendation with the understanding that the 295 members who currently hold that status will be permitted to retain it. The Board referred this action to the Committee on Constitution and Bylaws for appropriate changes to the Constitution and Bylaws. Pending such changes, the Board approved the recommendation that no new applicants for this category be accepted.

Membership/Fiscal Issues

The Committee on Membership, in conjunction with the Assembly Committee on Recruitment/Retention and Membership Affairs, discussed in depth the fiscal and organizational factors that affect dues levels and, consequently, membership retention. The consensus was that these factors have multiple causes and must be considered in the context of the Association's overall financial and programmatic planning.

Items recently reviewed by both membership committees, such as an action paper from Area VI regarding membership dues and the increasing number of members who will become eligible for the dues-exempt Life category in the next decade (by meeting the "95" requirement, i.e., age plus years of membership), are symptomatic of grass-roots concerns. It seems evident that these membership-related matters can be addressed best by a coordinated effort.

Valuable input was received from the Medical Director and leaders in the organizational structure, e.g., the APA Budget Committee, the Assembly Committee on Planning, and area representatives. This input convinced both membership committees that a more comprehensive review of membership, the budget, and future trends is necessary before knowledgeable decisions can be made, and they recommended appointment of an ad hoc committee to study these related issues. The Assembly approved such a committee in November 1989, and the Board gave its approval in December.

The Ad Hoc Committee on Membership and Fiscal Policies, Michael Vergare, M.D., chairperson, has already held several meetings. This committee includes representatives from membership and budget components and the planning bodies for the Assembly and the Board. Further, the action item from Area VI regarding a cap on APA dues and the action item from the Assembly Committee on Planning concerning the rule of 95 were referred to this committee for action. APA immediately undertook an actuarial analysis of the changing composition of its membership that projected demographic changes—e.g., more young psychiatrists and more members who will be eligible for Life status—and the corresponding impact on dues. The recommendations of the ad hoc committee were presented to the Assembly in May 1990 and to the Board in June.

Members-in-Training Who Fail to Advance

All district branches were asked to respond to the proposal that the "Operations Manual of the Board of Trustees" be revised to reflect a time limit for terminating the membership of Members-in-Training who fail to advance to General Member status (53 district branches responded to the survey; 48 agreed with the proposal and five disagreed). The operations manual, in the chapter on membership, states that "District Branches shall have the responsibility to . . . advance Members-in-Training to General Membership following completion of an approved psychiatric residency program . . . . If a physician does not cooperate with the District Branch by providing the information necessary for advancement, the branch may take steps to terminate his/her membership in that society, and consequently in the APA."

The proposed revision to the operations manual included the following wording: "This action may be implemented by the District Branch at any time after completion of residency, and must be implemented no later than one year after completion (e.g., a member completing training in June of 1990 could be dropped from the APA rolls at any time after that date, but no later than June of 1991 if he/she has not provided the information necessary for advancement)." The Board of Trustees approved this change.

APA will continue to provide the district branches with rosters of their members who need to advance throughout the year. In January 1990 the Office of Membership sent 72 of the 76 district branches lists of Members-in-Training who might need to advance to General Membership. Extensive follow-up, including letters to district branches presenting special problems with regard to advancements, will continue.

Dues Amnesty for Former Members

The Assembly Committee on Recruitment/Retention and Membership Affairs and the Committee on Membership recommended a one-time amnesty for members who wish to rejoin during 1990. This proposal was approved by the Assembly in November 1989 and by the Board of Trustees in December. The amnesty forgives APA and district branch dues in excess of 1 year's debt. Members seeking reinstatement are required to pay the more distal dues owed at the time of membership termination. The amnesty applies to only those who owe dues for years before 1988.

Membership/Ethics Issues

Membership-related ethics guidelines for operations manual. The committee discussed several membership/ethics issues with Dr. McDevitt, chairperson of the APA Ethics Committee, and the committee recommended that the following changes be incorporated into the "Operations Manual of the Board of Trustees."

1. An ethics investigation will not affect a member's eligibility to transfer to Life status before resolution of the investigation.

2. If a member fails to pay APA membership dues while an ethics

investigation is being conducted, the member's district branch may request that the membership termination be delayed until resolution of the ethics investigation. A written request must be submitted by the district branch to the APA Office of Membership.

3. If a district branch submits a Fellowship nomination to the APA Committee on Membership while ethical issues are pending, the committee will disregard any information concerning these matters other than a formal request from the district branch to withdraw the nomination.

The Board of Trustees approved these points for inclusion in the operations manual.

Revoking Fellowship for members who are suspended. The committee referred to the Ethics Committee the following recommendation: "If a Fellow is suspended, Fellowship is to be permanently revoked. If a member is suspended, he/she will be permanently ineligible to be nominated for Fellowship." There was strong sentiment among the committee members that Fellowship is a high honor, awarded for demonstrated and sustained standards of excellence. A suspension indicates a violation of these criteria and is not compatible with continuation of or consideration for the honor of Fellowship. The committee recognizes that these additional consequences of suspension increase its severity and may have an impact on the district branch's decision to recommend suspension. Accordingly, the committee recommended that these proposals be referred to the Ethics Committee for further discussion. The Board approved this referral.

Reporting the name of a member whose membership is terminated for nonpayment of dues during an ethics investigation. The committee recommended that this issue be referred back to the Ethics Committee for discussion and disposition. The Board approved the referral.

Years of suspension and credit toward Life status. Currently, the years of a member's suspension are included in determination of eligibility for Life status. The committee recommended to the Ethics Committee that a member not be allowed to count the years he or she is suspended toward the required 95 years of age plus membership. The Board approved referring the issue to the Ethics Committee.

Continued Eligibility for Inactive Status

Attention was given to the issue of members who have been granted permanent Inactive status and who remain in that category indefinitely even though continuing as an Inactive member may not be justified. Historically, Inactive status has been reserved for those who are experiencing severe hardship, either financially or medically, or are no longer practicing psychiatry. There appear to be more members who are requesting transfer to this status for reasons that do not appear to be permanent. The committee also expressed concern about the extension of benefits, such as insurance plans, to those with Inactive status.

The committee would like the operations manual to state that the situations of members with Inactive status will be reviewed every 5 years to determine if continuation of that status is appropriate. This review would be handled by the district branches, which would be assisted by the Office of Membership. The Board of Trustees approved this recommendation.

Membership Processing

The following actions were approved by the Board of Trustees.

Request for Associate Membership. The Committee on Membership recommended denial of an application for Associate Membership submitted by the Westchester County district branch; the denial was based on the Board's decision in December 1988 that no new applicants for Associate Membership be accepted pending further study of the category and the committee's recommendation in December 1989 that this category of membership be abolished.

Request to maintain Medical Student Member status. The committee recommended denial of a request from a Medical Student Member in the Southern California Psychiatric Society for permission to remain an APA member while completing an internal medicine residency (expected to end in June 1991). The committee recommended denial of his request as he does not fulfill the require-

ments for membership as either a Medical Student Member (since he has graduated from medical school) or a Member-in-Training (since he is not enrolled or accepted in a psychiatry residency program). He has been encouraged to reapply when eligible and to maintain his link with APA through subscriptions to the *American Journal of Psychiatry* and *Psychiatric News*.

Requests for review of General Membership eligibility. The Committee on Membership reviewed two applications for General Membership. The committee felt that the application submitted by the Western New York Psychiatric Society fulfilled the requirements for postgraduate training, but the committee recommended deferral of a decision until a copy of the New York State registration certificate is received.

The committee also reviewed an application for General Membership submitted by the Northern California Psychiatric Society. It recommended deferral of a decision until the district branch has further verified the applicant's credentials and licensure.

Requests for exemption from dual membership requirement. The committee reviewed two requests, one from a member of the Southern California Psychiatric Society and one from a member of the San Diego Society of Psychiatric Physicians, for exemption from the dual APA/district branch membership requirement. The committee recommended denial of their requests and continues to uphold the importance of members' integration in their district branches.

Fellowship nominations. The committee received 243 nominations for Fellowship from the district branches and reviewed 241; one request for a waiver of the 8-year General Member requirement and one request for waiver of the 2-year waiting period for resubmission were denied.

Of the 241 nominations reviewed, 207 (85.9%) were recommended for approval by the Board of Trustees. The approval rates in 1988 and 1987 were 87.1% and 88.0%, respectively. The committee recommended that 204 nominees for advancement from General Member to Fellow be approved, three nominees for advancement from Life Member to Life Fellow be approved, and decisions on 34 nominees for advancement from General Member to Fellow be deferred.

Nomination for Honorary Fellowship. In accordance with the "Operations Manual of the Board of Trustees," the Committee on Membership acts on each nomination by a voting member of the Association for Honorary Fellow or Distinguished Fellow and forwards its recommendation to the Board of Trustees. A letter nominating Ralph C. Kelzer for Honorary Fellowship was received from two Life Fellows of APA. The committee reviewed three additional letters of support and recommended approval of Mr. Kelzer for Honorary Fellowship. The Board of Trustees approved the nomination.

Referral of nomination for Honorary Fellowship to Committee on Membership. A letter was received from an APA Fellow nominating an individual for Honorary Fellowship. The operations manual states that the names of nominees and information concerning them must be circulated among the members of the Board of Trustees before any consideration by the Committee on Membership so that individual and confidential comments can be considered. In keeping with this policy, the Board of Trustees reviewed this nomination and referred it to the Committee on Membership.

Corresponding Members/Fellows and Members-at-Large. The committee reviewed applications for membership or advancement and recommended that 29 applications for Corresponding Membership be accepted, three nominations for advancement from Corresponding Member to Corresponding Fellow be approved, eight nominations for new Corresponding Fellow be approved, the decision on one nomination for advancement from General Member-at-Large to Fellow-at-Large be deferred, three applications for General Member-at-Large be approved, and one application for advancement from Associate Member-at-Large to General Member-at-Large be approved.

APA dues arrears and membership termination. In April 1989, 1,465 letters over the signature of the APA Treasurer were mailed to members who were in arrears for their 1988 APA dues. In July 1989, 1,086 certified letters over the signature of the APA Treasurer were mailed to those who had not responded to the earlier mailing. Extensive retention efforts were conducted in the ensuing months,

thereby minimizing membership losses; special emphasis was placed on personalized communication with members and district branches. The committee recommended and the Board approved in December 1989 dropping from APA membership the members whose dues were still in arrears for 1988 and administrative reinstatement of those who returned to good standing by Jan. 31, 1990, and were also in good standing in their district branches. At the end of 1989, 412 members were notified that their membership had been terminated and were given a 1-month grace period to pay their dues and be administratively reinstated; 30 members responded during the grace period. In April 1990, nearly 1,700 members received letters from the Treasurer officially notifying them that they had not paid their 1989 APA dues.

Resignations. The committee reviewed the names of members who had resigned. Under standing authorization of the Board of Trustees, the Medical Director regretfully accepted the resignations. The 211 resignations in 1989 by member class and as a percentage of total resignations were as follows: Medical Student Member, N=36 (17.1%), Member-in-Training, N=36 (17.1%), General Member, N=128 (60.7%), Associate Member, N=1 (0.5%), Fellow, N=9 (4.3%), Life Member, N=1 (0.5%).

Dropping of members dropped by district branches. Chapter 8 of the Bylaws states, "Resignation or loss of membership in the Asso-

ciation or the member's District Branch for any reason shall entail loss of membership in both." The names of members who had resigned from or been dropped by their district branches were reviewed by the APA Committee on Membership. They had been advised that loss of branch membership would involve loss of APA membership. The committee recommended that the Board of Trustees authorize dropping these members from APA membership as of December 1989 and that the Board of Trustees authorize administrative reinstatement of those who return to good standing in their district branches and are also in good standing in APA.

Dues relief and Inactive status. At its November meeting, the committee reviewed requests for dues relief and/or transfer to Inactive status. It recommended that 18 requests for special consideration be deferred pending district branch recommendation, 119 waivers of dues be approved, 40 requests for transfer to Permanent Inactive Membership be approved, six requests for transfer to Temporary Inactive status be approved, 17 requests for dues reduction be approved, two requests for deferment of dues be approved, one request for refund of dues be approved, and 29 requests for dues relief or Inactive status be denied.

Between 1982 and 1989 there was a 92.7% increase in the total number of dues relief requests, from 165 to 318. The approval rate decreased slightly, from 88.5% to 83.3%.

Report of the Committee of Tellers

Edward C. Kirby, Jr., M.D., Chairperson

The Committee of Tellers met on April 5, 1990, at APA headquarters to certify the results of the 1990 election. Ballots were mailed on Feb. 20, 1990, to 33,733 eligible voting members. From that number were deducted 117 undeliverable ballots. The adjusted number of eligible voting members was 33,616, and 14,076 ballots (41.9%) were returned and included in the final tally.

The Committee of Tellers reviewed a special report from staff concerning a small number of duplicate ballots that were sent to members with the 981 zip code prefix in Washington state. The committee verified that the margin of votes in all national races was large enough that any duplicate voting could have made no difference.

The committee acted on uncertain votes that had been held for their decisions. It also ascertained that all candidates had verified the accuracy of their biographical statements and had submitted the required statements of compliance with election guidelines.

The Committee of Tellers certified that the following individuals were elected to office and so reported to the Board of Trustees— President-Elect: Lawrence Hartmann, M.D. (53.6% of the votes cast), Vice-President: John S. McIntyre, M.D. (52.5%), Treasurer: Mary Jane R. England, M.D. (53.1%), Trustee-at-Large: Jerry M.

Wiener, M.D. (54.5%), Member-in-Training Trustee-Elect: Karen A. Abrams, M.D. (53.2%), Area II Trustee: Harvey Bluestone, M.D. (65.2%), and Area V Trustee: Harvey R. St. Clair, M.D. (50.3%).

To have a valid vote on changes to the Constitution and Bylaws, 33⅓% of the eligible voting members must cast votes. Abstain and invalid votes are considered to be votes cast and count toward determining if 33⅓% has been reached. Abstain and invalid votes do not count in determining whether a change passes or fails. Once 33⅓% has been reached, a majority must approve amendments to the Bylaws. In the vote on whether to amend chapter 3.1 of the Bylaws, 37.9% of the eligible voters cast votes. Of those votes, 97.6% were in favor, so the amendment passed. The change allows the Speaker-Elect to vote in the absence of the Speaker at Board meetings.

The Committee on Tellers recommended that the Board of Trustees accept the results of the 1990 election, and the Board accepted them. The Board also approved a recommendation by the Committee of Tellers to dispose of the ballots from the 1990 election after the 1990 annual meeting.

1989–1990 Annual Report
of the American Board of Psychiatry and Neurology, Inc.

Composition of the Board

At its business meeting in November 1989, the American Board of Psychiatry and Neurology (ABPN) elected the following officers, who began their terms on Jan. 1, 1990: Dr. Layton McCurdy, President; Dr. Elliott Mancall, Vice-President; Dr. William Bell, Secretary; Dr. Maurice J. Martin, Treasurer; and Dr. John F. McDermott, Jr., Executive Committee member-at-large.

Dr. Kenneth Altshuler, M.D. (Dallas), nominated by the American Medical Association, was elected to a 3-year term on the board to succeed Dr. William Webb, who completed his second 4-year term on the board on Dec. 31, 1989. Dr. Peter Tanguay, M.D. (Los Angeles), nominated by the American Psychiatric Association, was elected to a 4-year term on the board to succeed Dr. Robert Michels, who completed his second 4-year term on the board on Dec. 31, 1989. Dr. Stuart A. Schneck, nominated by the American Neurological Association, was renominated and reelected to serve a second 4-year term as a neurology director. The names of the 1990 ABPN directors follow; those serving second 4-year terms are not eligible for reelection.

Nominated by the American Medical Association (psychiatry directors): Dr. Kenneth Z. Altshuler, M.D. (first term expires Dec. 31, 1992), Dr. Maurice J. Martin (second term expires Dec. 31, 1991), and Dr. John F. McDermott, Jr. (second term expires Dec. 31, 1990).

Nominated by the American Psychiatric Association (psychiatry directors): Dr. Layton McCurdy (second term expires Dec. 31, 1990), Dr. James H. Shore, M.D. (first term expires Dec. 31, 1990), Dr. Peter E. Tanguay (first term expires Dec. 31, 1993), Dr. Lenore C. Terr (first term expires Dec. 31, 1991), and Dr. Gary J. Tucker (second term expires Dec. 31, 1992).

Nominated by the American Neurological Association (neurology directors): Dr. William E. Bell (second term expires Dec. 31, 1991), Dr. J. Donald Easton (second term expires Dec. 31, 1992), Dr. Ludwig Gutmann (first term expires Dec. 31, 1990), and Dr. Stuart A. Schneck (second term expires Dec. 31, 1993).

Nominated by the American Academy of Neurology (neurology directors): Dr. Mark L. Dyken, Jr. (first term expires Dec. 31, 1992), Dr. Elliott L. Mancall (second term expires Dec. 31, 1990), Dr. N. Paul Rosman (second term expires Dec. 31, 1990), and Dr. Jack P. Whisnant (second term expires Dec. 31, 1990).

Dr. Stephen C. Scheiber is the Executive Vice President of the ABPN; his title was changed from Executive Secretary during 1989.

Examinations

Part I. At the part I (written) examination on April 3, 1990, 2,108 psychiatrists were examined; 1,244 (59%) passed and 864 (41%) failed. A total of 723 neurologists (including child neurologists) were examined; 365 (50%) passed and 358 (50%) failed. Table 1 contains the numbers of candidates in each year from 1985 to 1990. The next part I examination will be held on April 2, 1991. Applications for that examination are due no later than Sept. 1, 1990.

Geriatric psychiatry. The first examination for certification in psychiatry with added qualification in geriatric psychiatry will be held in concert with the next part I examination, to be held on April 2, 1991. This will be a half-day written examination.

Part II. At the 1989 part II (oral) examinations held in Baltimore (April 10–11), Denver (June 10–11), and Boston (Nov. 13–14), 1,560 psychiatrists, 466 neurologists, and 69 child neurologists were examined. For statistics on these examinations, refer to table 2. The examination sites for 1990 are Seattle (March 12–13), Minneapolis (June 11–12), and Washington, D.C. (Oct. 29–30).

The current fees for examination are as follows: part I examination fee=$550, part I reexamination fee=$300, part II examination

TABLE 1. Candidates for ABPN Part I (Written) Examination, 1985–1990

Physician Status	Number of Candidates					
	1985	1986	1987	1988	1989	1990
Met requirements	2,506	2,703	2,649	2,861	3,134	3,213
Accepted examination	2,409	2,574	2,477	2,782	3,092	3,142
Took examination	2,167	2,301	2,255	2,471	2,725	2,831

fee=$400, part II reexamination fee (failure of major or major and minor)=$400, part II reexamination fee (failure of minor)=$300.

Board Decisions and Items of Interest

1. At its September 1989 meeting, the American Board of Medical Specialties approved the application of the ABPN for certification with added qualification in geriatric psychiatry. The Committee on Certification for Added Qualification in Geriatric Psychiatry was appointed in November 1989 and held its first meeting in December 1989. For 1990, the committee membership includes M.J. Martin, M.D. (ABPN psychiatry director, Rochester, Minn., chairperson, 3-year term); Gabe Maletta, M.D. (geriatric psychiatrist, Minneapolis, vice-chairperson, 6-year term); Gene Cohen, M.D. (geriatric psychiatrist, Washington, D.C., secretary-treasurer, 4-year term); Eric Caine, M.D. (geriatric psychiatrist, Rochester, N.Y., 5-year term); Elliott L. Mancall, M.D. (ABPN neurology director, Philadelphia, 2-year term); and Gary J. Tucker, M.D. (ABPN psychiatry director, Seattle, 1-year term). All future appointments to the committee made by the ABPN will be for one 6-year term. Certificates issued will be 10-year time-limited certificates.

2. The ABPN passed the following motion concerning recertification: "Effective October 1, 1994, all individuals achieving Board Certification by the American Board of Psychiatry and Neurology, Inc. in Psychiatry, Neurology, Neurology with Special Qualification in Child Neurology, and Child and Adolescent Psychiatry will be issued 10-year time-limited certificates." The first recertification examination will be held no later than Jan. 1, 2000.

3. The ABPN changed Dr. Stephen C. Scheiber's title from Executive Secretary to Executive Vice President.

4. The ABPN hired Dorthea Juul, Ph.D., as its first full-time research coordinator effective June 1, 1990.

5. The ABPN revised its policy prohibiting participation as an ABPN examiner or member of an ABPN committee by an individual who has participated in so-called "Board review" courses, to include courses and written, video, or audio materials produced for the purpose of passing ABPN examinations. This policy was also revised to include individuals found to be in violation of ethical standards of their specialty society or societies.

6. The ABPN reaffirmed its policy whereby all licensing and training requirements must be met before application for examination. The only exception is for residents who complete training after Sept. 1 but before Oct. 1. Such applicants may submit applications by the Sept. 1 deadline only if they contact the Board office in writing before July 1 to obtain information regarding special application procedures.

7. The ABPN reaffirmed its policy whereby every applicant must have an *unlimited* license to practice medicine in a state, commonwealth, or territory of the United States or a province of Canada. Every applicant is required to submit copies of current license reg-

TABLE 2. Performance of Physicians Who Took ABPN Part II (Oral) Examinations in 1989

Candidate Group	Total					Graduates of Schools in U.S. or Canada					Graduates of Foreign Medical Schools				
		Passed and Were Certified		Failed			Passed and Were Certified		Failed			Passed and Were Certified		Failed	
	N	N	%	N	%	N	N	%	N	%	N	N	%	N	%
All specialties	2,095	1,300	62	795	38	1,532	1,065	70	467	30	563	235	42	328	58
New candidates	1,485	991	67	494	33	1,129	825	73	304	27	356	166	47	190	53
Reexamined	610	309	51	301	49	403	240	60	163	40	207	69	33	138	67
Psychiatry	1,560	930	60	630	40	1,127	777	69	350	31	433	153	35	280	65
New candidates	1,103	721	65	382	35	833	610	73	223	27	270	111	41	159	59
Reexamined	457	209	46	248	54	294	167	57	127	43	163	42	26	121	74
Neurology	466	327	70	139	30	359	261	73	98	27	107	66	62	41	38
New candidates	331	238	72	93	28	262	195	74	67	26	69	43	62	26	38
Reexamined	135	89	66	46	34	97	66	68	31	32	38	23	61	15	39
Child neurology	69	43	62	26	38	46	27	59	19	41	23	16	70	7	30
New candidates	51	32	63	19	37	34	20	59	14	41	17	12	71	5	29
Reexamined	18	11	61	7	39	12	7	58	5	42	6	4	67	2	33

istrations and expiration dates with the application, in addition to documentation of all training.

8. Documentation for training submitted with part I applications must include exact dates of training. The ABPN will accept only certificates that include precise training in the specialty in which the applicant seeks certification. Certificates that state, for example, "resident in Internal Medicine/Psychiatry" or other dual statements will not be accepted as documentation of psychiatry training by the ABPN.

9. The ABPN is proceeding with plans to offer examination for certification in neurology with added qualification in clinical neurophysiology. Final approval by the American Board of Medical Specialties is anticipated, pending letters of support from various specialty societies and other certification boards within the American Board of Medical Specialties.

10. The ABPN held a conference in July 1989 that focused on certification and recertification and emphasized lifetime learning and the educational process. Several organizations were represented, and four recommendations came out of the conference: 1) that the ABPN approve a process for recertification, including time-limited certification, 2) that the ABPN invite participation in an interorganizational task force on written examinations, 3) that the ABPN develop a research coordinator position within its national office, and 4) that the ABPN explore with relevant organizations the feasibility of holding the part I examination closer to or before completion of residency. After the conference the board acted on all of the recommendations. Actions on the recertification and research coordinator issues were mentioned earlier in this report. Regarding item 2, the ABPN established an interorganizational task force, which is currently discussing written examinations. The ABPN has referred the issue of timing for the part I examination to the field.

11. At the 1989 APA annual meeting, the ABPN offered a workshop titled "ABPN Recertification." The ABPN psychiatry directors presented information and responded to questions. In addition, the Executive Vice President and psychiatry directors have participated in plenary sessions and other workshops of APA and the American Association of Directors of Psychiatric Residency Training in an attempt to clarify information and to publicize current issues of interest. A workshop on recertification will be held at the 1990 APA annual meeting.

12. At the fall 1989 meeting of the American Neurological Association and the spring 1990 meeting of the American Academy of Neurology, ABPN neurology directors and the Executive Vice President met with the Association of University Professors of Neurology to discuss current issues of interest to the ABPN and to respond to questions. This meeting proved valuable in outlining the ABPN's current policies and training requirements. Recertification was a key point of discussion, as was advising the Association of University Professors of Neurology of continuing deliberations regarding possible ABPN designation of neurophysiology as a subspecialty.

TABLE 3. Performance of Physicians Who Took Oral Examinations in Child and Adolescent Psychiatry in 1989

Candidate Group and Performance	Total		Graduates of Schools in U.S. or Canada		Graduates of Foreign Schools	
	N	%	N	%	N	%
Total	235	100	211	90	24	10
Pass	134	57	125	59	9	38
Condition	32	14	26	12	6	25
Fail	41	17	33	16	8	33
Fail, must reapply	28	12	27	13	1	4
New candidates	175	74	153	87	22	13
Pass	102	58	94	61	8	37
Condition	32	18	26	17	6	27
Fail	41	23	33	22	8	36
Reexamined candidates	60	26	58	27	2	8
Pass	32	53	31	53	1	50
Fail, must reapply	28	47	27	47	1	50

13. The ABPN history continues to be updated by Dr. Marc Hollender, who is being assisted by Drs. Helen Beiser, William Bell, John Kurtzke, N. Paul Rosman, Stephen Scheiber, S. Mouchly Small, James Sussex, William Webb, and Dewey Ziegler.

Committee on Certification in Child and Adolescent Psychiatry

Members of the Committee on Certification in Child and Adolescent Psychiatry are elected to serve one 6-year term each and are not eligible for reelection. The members of the 1990 Committee on Certification in Child and Adolescent Psychiatry are Dr. Joel Zrull, chairperson (Toledo, Ohio, term expires Dec. 31, 1991); Dr. Theodore Shapiro, vice-chairperson (New York, term expires Dec. 31, 1993); Dr. Lois T. Flaherty, secretary-treasurer (Baltimore, term expires Dec. 31, 1993); Dr. Catherine DeAngelis, representative from the American Board of Pediatrics (Baltimore, term expires Dec. 31, 1994); Dr. Thomas M. Haizlip (Raleigh, N.C., term expires Dec. 31, 1995); Dr. Kenneth Robson (Hartford, Conn., term expires Dec. 31, 1994); and Dr. William H. Sack (Portland, Ore., term expires Dec. 31, 1992).

At its Sept. 15–17, 1989, examination in Atlanta, the Committee on Certification in Child and Adolescent Psychiatry examined 235 candidates; 134 (57%) passed, 32 (14%) conditioned the examination, and 69 (29%) failed or failed and must reapply. For additional

statistics refer to table 3. The 1990 examination will be held Sept. 7–9, 1990, in Denver. The 1991 examination will be held Sept. 20–22, 1991, in Baltimore. Applications are due by the May 1 preceding the examination and are available from the American Board of Psychiatry and Neurology, Inc., 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015.

The current fees for examination are as follows: application fee=$225, oral examination fee=$450, oral reexamination fee (condition)=$350, oral reexamination fee (failure)=$450, written examination or reexamination fee=$275.

Applicants are required to submit copies of current license registrations and expiration dates with their applications, in addition to documentation of all training. All licensing and training requirements must be met before application for examination.

Other items of interest and decisions made by the Committee on Certification in Child and Adolescent Psychiatry are as follows:

1. The committee passed a motion stating that it will follow the ABPN's recertification plans and will work within the same time frame.

2. The committee continues to arrange examinations in a weekend format. This format has been received positively by the overwhelming majority of candidates, examiners, and host facilities.

3. The committee continues to note difficulties with certificates issued to residents. If child psychiatry training is done during general residency it must be designated as such.

Committee on Certification for Added Qualification in Geriatric Psychiatry

The members of this committee were listed earlier in this report. The first examination will be held April 2, 1991. Completed applications are due the Sept. 1 preceding the examination and are available from the American Board of Psychiatry and Neurology, Inc., 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015. The current fees for examination are as follows: examination fee=$725, reexamination fee=$500. General requirements are as follows:

1. Candidates must be certified in general psychiatry.

2. All licensing and training requirements must be met before the applicant applies for examination.

3. A formal application on the original form must be completed and filed by the deadline.

4. Applicants must have completed a 1-year fellowship in geriatric psychiatry beginning no sooner than postgraduate year 5, which must be documented by a letter from the training director. For the first 5 years admission to examination may also be achieved by those who follow a clinical pathway, spending 25% of their practice time with geriatric patients, as an alternative to completing a 1-year geriatric fellowship.

5. After the initial 5-year period, applicants will be accepted for examination only if they have successfully completed a 1-year fellowship program in geriatric psychiatry approved by the Accreditation Council for Graduate Medical Education.

Certificates will be issued for a 10-year time-limited period, after which recertification will be necessary to maintain active certification. Examinations will be given once a year or once every other year, depending on the number of candidates. For additional information the "Information for Applicants for Certification in Added Qualification in Geriatric Psychiatry" may be obtained by contacting the ABPN office at 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015.

The American Board of Psychiatry and Neurology, Inc.: Report on the 1989 Examinations

The following successfully completed the Board examination in April 1989.

PSYCHIATRY

Mary Beth Ackerley, M.D., Owings Mills, MD
David Naftali Adler, M.D., Lawrence, NY
Robert Michael Altman, M.D., Alexandria, VA
Lori Lynn Altshuler, M.D., Cabin John, MD
Harold Amsel, M.D., New York, NY
Luis C. Ang, M.D., New York, NY
Edward Stanley Arnold, M.D., Nashville, TN

Madeleine R. Barris, M.D., Bronx, NY
Lonny J. Behar, M.D., New York, NY
Beth Anne Bernstein, M.D., Salt Lake City, UT
Purabi Bharatiya, M.D., Scotch Plains, NJ
Susan Gail Blank, M.D., Metuchen, NJ
Harry Andrew Brandt, M.D., Baltimore, MD
Keith A. Brown, M.D., Bellevue, WA
Raul Rodolfo Burciaga, M.D., Indianapolis, IN

Andres Tomas Cabrero, M.D., New York, NY
Joseph Richard Calabrese, M.D., Shaker Heights, OH
Pamela Ullman Call, M.D., New York, NY
Marian Patricia Callaghan, M.D., Marlton, NJ
Ana Elisa Campo-Bowen, M.D., Coral Gables, FL
Frank Remo Cancellieri, M.D., Brooklyn, NY
Francis Joseph Capobianco, M.D., San Diego, CA
John Alexander Cervantes, M.D., Ventura, CA
James C-Y Chou, M.D., Orangeburg, NY
Josiane Claude Cobert, M.D., Westfield, NJ
Mary Ellen Cody, M.D., Baltimore, MD
Howard Jay Cohen, M.D., Alexandria, VA
Alan Bertrand Compton, M.D., Silver Spring, MD
David Oliver Conant-Norville, M.D., Pendleton, OR
Steven Jay Cooper, M.D., Monsey, NY
Patricia Perry Corke, M.D., Houston, TX
Michael Francis Costanzo, M.D., Katonah, NY
Janis Lynne Cutler, M.D., New York, NY

Charles Talcott Davis, M.D., New York, NY
Jayakanthi DeAlwis, M.D., Short Hills, NJ
John Austin DeFrate, M.D., Crownsville, MD
Lois May DeRitter, M.D., Middlesex, NJ
Bert Ludig Dech, M.D., Port Washington, NY
Anthony Joseph Dowling, M.D., Warwick, RI
John McCall Downs, M.D., Memphis, TN
Erica Joan Duncan, M.D., New York, NY
Stephanie Susan Durruthy, M.D., Columbia, MD

Michael Frederick Egan, M.D., Chevy Chase, MD
Cherie I. Elfenbein, M.D., Staten Island, NY
Mark David Epstein, M.D., New York, NY

Christopher A. Fabian, M.D., New York, NY
Stephen Feld, M.D., New York, NY
Alan David Felix, M.D., New York, NY
Jeffrey Scott Fine, M.D., New York, NY
Michael Bruce First, M.D., New York, NY
Stephen Fisher, M.D., Oakland, CA
Michael Alan Flaum, M.D., Iowa City, IA
Lewis Andrew Fox, M.D., New York, NY
Thomas South Fox, M.D., Concord, NH
Jeffrey Bruce Freedman, M.D., Bronx, NY
Nelson Bruce Freimer, M.D., New York, NY
Richard Alan Friedman, M.D., New York, NY

H. Jordan Garber, M.D., Los Angeles, CA
William Robert Geckeler, M.D., Temecula, CA

Richard Jay Gersh, M.D., New York, NY
Jed Cory Goldart, M.D., New York, NY
Ian Simon Goldberg, M.D., New York, NY
Stephen Alan Goldman, M.D., Indianapolis, IN
Maria Isabel Goldstein, M.D., Woodland Hills, CA
Pearl Jade Gong, M.D., New York, NY
Alan Gordon, M.D., Providence, RI
Ellen Frances Gottheil, M.D., Mountain View, CA
Brian Saul Grobois, M.D., Forest Hills, NY
Elisabeth Benson Guthrie, M.D., Ossining, NY

Ba Han, M.D., Ogdensburg, NY
William Henry Hankin, Jr., M.D., Cape May Court House, NJ
Julie Anne Hatterer, M.D., New York, NY
Shrikant M. Hatwalkar, M.D., Cambridge, OH
Carolyn Romaine Haynie, M.D., Laurel, MD
Eric Lee Heiligenstein, M.D., Madison, WI
David Poythress Heilner, Jr., M.D., Cumberland Foreside, ME
Phillip G. Helding, D.O., Hinsdale, IL
Merrill Scot Herman, M.D., White Plains, NY
Judith Herzig, M.D., Pound Ridge, NY
Frederick Gilbert Hicks, M.D., Kirkwood, MO
Janet Rae Hoveland, M.D., Silver Spring, MD
Emmanuel Hriso, M.D., Union City, NJ

Daniel C. Javitt, M.D., Riverdale, NY
Paul Jayson, M.D., New York, NY
Michael Lewis Jefferies, M.D., Baltimore, MD
Sonali D. Jeste, M.D., La Jolla, CA
Brian Johnson, M.D., Newtonville, MA
Joyce Marie Johnson, M.D., Chevy Chase, MD
Jeffrey Scott Jones, M.D., San Francisco, CA

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Oren Kalus, M.D., New York, NY
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Mark Kutcher, M.D., Nashville, TN
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Kenneth Walter Lajewski, M.D., Pittsford, NY
J. Steven Lamberti, M.D., Rochester, NY
Joshua Baumol Lamm, M.D., West Hempstead, NY
Brian Augustine Lawlor, M.D., Bethesda, MD
Wing-Ki Lee, M.D., Marina Del Rey, CA
Dennis Leone, M.D., Sewell, NJ
Paul Kahing Leung, M.D., Gresham, OR
Marc Steven Levine, M.D., Rockville, MD
Mark David Levine, M.D., San Francisco, CA

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Stephen Timothy Lincks, M.D., Massapequa Park, NY
Jill Robin Linder, M.D., New York, NY
Louis S. Linfield, M.D., New York, NY
Martin S. Lipschutz, M.D., Amityville, NY
Robert Lowinger, M.D., Flushing, NY
Roberta Moloff Luft, M.D., Hockessin, DE
Peter Jay Lusche, M.D., Tucson, AZ
Dwight Howard Lysne, M.D., Fargo, ND

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Dolores Malaspina, M.D., Englewood, NJ
Mary Margaret Maloney, M.D., Indianapolis, IN
Cecile Leguir Many, M.D., New Orleans, LA
Dennis C. Marcus, M.D., Great Barrington, MA
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Peter Michael Marzuk, M.D., New York, NY
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Marcos Rafael Nieves, M.D., Delmar, NY

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Margot Susan Rubinstein, M.D., White Plains, NY
Lili Rysz, M.D., New York, NY

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Carla Ann Sarno, M.D., Bel Air, MD
Frederick Warren Schaerf, M.D., Baltimore, MD
Michele Scheiner, M.D., Peakskill, NY
Franklin Richard Schneier, M.D., New York, NY
Howell Evan Schrage, M.D., Riverdale, NY
Robert David Schults, M.D., Anchorage, AK
Alina Segura-Bustamante, M.D., Brooklyn, NY
Ira Mark Shapiro, M.D., Lewiston, ME
Alison Mary Sheridan, M.D., Waltham, MA
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Stephen Laurence Snyder, M.D., Brooklyn, NY
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Daniel Lloyd Sussman, M.D., New York, NY

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Marion Melanie Worthington, M.D., Houston, TX
Joseph Chong-Sang Wu, M.D., Garden Grove, CA
Bezalel Wurzberger, M.D., Glens Falls, NY

Donna D. Yi, M.D., New City, NY

Sarah Rachel Zamari, M.D., Providence, RI

NEUROLOGY

Cecily Maciakal Anto, M.D., Dix Hills, NY
Everett J. Austin, M.D., San Francisco, CA

Phillip Ault Ballard, Jr., M.D., Seattle, WA
Edward Barry Bromfield, M.D., Boston, Ma

Vinay Chaudhry, M.D., Perry Hall, MD
Ali Khalil Choucair, M.D., Marshfield, WI

Elias Dickerman, M.D., Grants Pass, OR
Michael Gerard Dunn, M.D., Pittsford, NY

Charles Richard Effron, M.D., New York, NY
Avrom David Epstein, M.D., Lexington, KY

Stewart Alan Factor, D.O., Albany, NY
Elaine Rose Feraru, M.D., North Hollywood, CA
Noel Ronnie Fleischer, M.D., New York, NY
Gary Seth Friedman, M.D., Oklahoma City, OK

Dana Helga Gabuzda, M.D., Boston, MA
Michael Joseph Giuliani, M.D., Glenshaw, PA
Daniel Richard Glor, M.D., Silver Spring, MD
Malcolm Howard Gottesman, M.D., Bellerose, NY

Michael Alan Hillman, M.D., Marshfield, WI

Joyce Ilson, M.D., Brooklyn, NY
Laura Marie Isensee, M.D., Washington, DC

Donald Ray Johns, M.D., Baltimore, MD

Bruce Alfred Kaplan, M.D., New York, NY
Marc Katchen, M.D., Galesburg, IL
Louis Carlton Kirby II, M.D., Glendale, AZ
Ranganna Kishore-Kumar, M.D., Takoma Park, MD

Ronald Fred Klinger, M.D., Massapequa, NY
Robert Sherman Knapp, M.D., Canandaigua, NY
Joseph Harold Kratzer, M.D., New York, NY

Hans Alfred Langsjoen, M.D., Galveston, TX
Carol Frances Lippa, M.D., Worcester, MA
Judith Pamela Lustig, M.D., Bronx, NY

Karen Sloane Marder, M.D., New York, NY
Kenneth Lee Marek, M.D., Baltimore, MD
Ajay Kumar Misra, M.D., Los Angeles, CA
Paul Lawrence Moots, M.D., New York, NY
Anne Mildred Moss, M.D., Rochester, NY

Elizabeth Ortof, M.D., Niskayuna, NY

George William Petty, M.D., Rochester, MN

Paula Deborah Ravin, M.D., Holden, MA
Stephen Geffry Reich, M.D., Baltimore, MD
Richard Seth Rosenberg, M.D., Morristown, NJ
Neil Stuart Rosenthal, M.D., New York, NY
Michael Rubin, M.D., Riverdale, NY

Ralph Lewis Sacco, M.D., New York, NY
Mahasukhlal H. Shah, M.D., Peoria, IL
Harold Raymond Smith, M.D., Irvine, CA
Lee Stuart Stein, M.D., Memphis, TN
Igor Stiler, M.D., Brooklyn, NY

Gilbert Stephan Tausch, M.D., Plymouth Meeting, PA
Kurt Florian Patrick Thomas, M.D., New York, NY

Glenn Even Waldman, M.D., Bayside, NY

Mark Julian Zuckerman, M.D., St. James, NY

NEUROLOGY WITH SPECIAL QUALIFICATION IN CHILD NEUROLOGY

Majeed Al-Mateen, M.D., Oakland, CA

Rose-Mary Naaman Boustany, M.D., Durham, NC

Sansnee Chatkupt, M.D., Livingston, NJ
Lucy Ann Civitello, M.D., Washington, DC

Radha Giridharan, M.D., Brooklyn, NY

Martin L. Kutscher, M.D., Goldens Bridge, NY

The following successfully completed the Board examination in June 1989.

PSYCHIATRY

Gil Bello Abelita, M.D., Peoria, IL
Veronica Alfero, M.D., Eugene, OR
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Man Mohan Anand, M.D., Parkville, MO
Neal Anzai, M.D., Honolulu, HI

Shamji P. Badhiwala, M.D., Waco, TX
James Guy Baker, M.D., Bellaire, TX

Elissa Mary Ball, M.D., Beulah, CO
Lawrence Estel Banta, M.D., Boise, ID
Robert Earl Barker, M.D., Agoura Hills, CA
Eduardo Barreto, M.D., San Diego, CA
Mary Garber Bartels, M.D., Seattle, WA
Alexander MacWhorter Beebee, M.D., Los Angeles, CA
Robert Holloway Bein, M.D., Safford, AZ
Iverson Charles Bell, Jr., M.D., Atlanta, GA
Lynn D. Bertram, M.D., Oakland, CA

Ilsa Joy Bick, M.D., San Antonio, TX
Howard Gary Blackstone, M.D., Petaluma, CA
Catherine Elizabeth Blanton Flowers, M.D., Houston, TX
Alan Scott Blaustein, M.D., Los Angeles, CA
Nashaat Nessim Boutros, M.D., Houston, TX
Patricia Kimberly Boyer, M.D., New Orleans, LA
Emily Susan Brewer, M.D., San Francisco, CA
Joekie Brouwer, M.D., Springfield, MO
George Richard Brown, M.D., Helotes, TX

Ronald Miles Burd, M.D., Fargo, ND
Joseph Hampton Burkett, M.D., Fort Worth, TX
Dana Andrew Butler, M.D., Lubbock, TX

Joseph Louis Calles, M.D., Alhambra, CA
Sue Ann Callison, M.D., Tucson, AZ
Normand Jean Carrey, M.D., Nepean, Ontario, Canada
Michael Alan Chan, M.D., Worthington, OH
Christine Yuanchen Chang, M.D., Palo Alto, CA
Richard Neil Ciasca, M.D., Glendale, CA
Lee Walter Clark, M.D., Denver, CO
Jeffrey Lane Clothier, M.D., Houston, TX
Alan Jay Cohen, M.D., San Francisco, CA
Richard Alan Cohen, M.D., Portland, OR
Ronald K. Cohen, M.D., Renton, WA
Seth Alexander Cohen, M.D., Seattle, WA
Cynthia Ann Coles, M.D., San Diego, CA
Jack S. Conway, M.D., Seattle, WA
Lawrence Edward Cormier, M.D., Shiprock, NM
Constance None Corson, M.D., Rocky Mount, NC
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David P. Easley, M.D., Louisville, KY
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Samira Mohamed Elnaggar, M.D., Arlington, TX
Mohamed I. Elyan, M.D., York, PA
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John Rune Evaldson, M.D., Albuquerque, NM
Linda Youngman Evans, M.D., Fort Gordon, GA
William Southall Evans, Jr., M.D., Fort Gordon, GA

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Patricia Ann Fangohr, M.D., Phoenix, AZ
Pablo Maria Jose Luis Farias, M.D., San Cristobal, Chiapas, Mexico
Marilyn Feder, D.O., Chicago, IL
Jay Richard Feierman, M.D., Albuquerque, NM
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Marian Fireman, M.D., Portland, OR
Patricio G. Fischman, M.D., New Haven, CT
Martin Benson Fisher, M.D., Raymondville, TX
Larry Flowers, M.D., The Woodlands, TX
Marcia R. Flugsrud-Breckenridge, M.D., Des Moines, IA
Eric Foxman, M.D., Pacific Palisades, CA
David Robert Franzblau, M.D., Manchester, MI
Susan Ray Frederick, M.D., Denver, CO
Jack P. Freinhar, M.D., Los Angeles, CA
Angelica Schilling Frias, M.D., Houston, TX

Bruce Martin Gainsley, M.D., Van Nuys, CA
Linda Kay Ganzini, M.D., Portland, OR
Theresa Suzanne Garton, M.D., Oklahoma City, OK
Debbie Christine Gee, M.D., Albuquerque, NM
Alexis Anne Giese, M.D., Denver, CO
Sally L. Godard, M.D., McMinnville, OR
Irwin Charles Goldberg, M.D., West Hollywood, CA
Joshua David Golden, M.D., San Diego, CA
David Joseph Goldmeier, M.D., Creve Coeur, MO
Theodore Avram Goodman, M.D., Sacramento, CA

Frank Henry Gowaty, M.D., Woodside, CA
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Esther Maria Gwinnell, M.D., Portland, OR

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Pamela G. Hamilton, M.D., Oklahoma City, OK
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Stanley Earl Harris, M.D., Los Angeles, CA
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Bruce Allen Kaup, M.D., Baltimore, MD
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Roy Johnson King, M.D., Stanford, CA
Daniel Ethan Klein, M.D., Seattle, WA
Linda Diana Klein, M.D., Cincinnati, OH
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John Thornton O'Donnell, M.D., New York, NY
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Steven Andrew Ornish, M.D., Le Mesa, CA
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Lauren Denise Parsons, M.D., Wichita Falls, TX
Rebecca Mote Peake, M.D., Dallas, TX
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Laurence John Pezor, Jr., M.D., El Cajon, CA
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Joan Frances Scheibel, M.D., Hawthorne, CA
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Pamela Seator, M.D., Overland Park, KS
Harvey Paul Segalove, M.D., Berkeley, CA
Valery Shikverg, M.D., Port Washington, NY
Thomas Merrill Shiovitz, M.D., Sherman Oaks, CA
Daniel J. Siegel, M.D., Los Angeles, CA
Jose Ramon Silvas, M.D., Yakima, WA
Robert Gordon Skwerer, M.D., Sarasota, FL
Judy Kay Snyder, M.D., Goshen, IN
Julia M. Soler, M.D., Baltimore, MD
Nabil N. Soliman, M.D., Los Angeles, CA
Marilyn M. Sosna, M.D., Santa Ana, CA
Ivan C. Spector, M.D., Houston, TX
David Martin Stein, M.D., Honolulu, HI

Douglas James Stockwell, M.D., Houston, TX
Deanna Sue Storts, M.D., Tulsa, OK
Victoria Stout, D.O., Layton, UT
David Lee Sultzer, M.D., Los Angeles, CA

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Douglas Eliot Tucker, M.D., Santa Monica, CA
Bruce Ira Turetsky, M.D., Piedmont, CA

Sarita B. Uhr, M.D., San Diego, CA
Guillermo Urrutia, M.D., New Orleans, LA

Craig Rooke Van Tuinen, M.D., Waterbury, VT
Russell Albert Vandenbelt, M.D., Bellevue, WA
Ashit Kanaiyalal Vijapura, M.D., Conyers, GA
Jennifer Griffith Vincent, M.D., Seattle, WA

Adel Wassef, M.D., Galveston, TX
Judith Leslie Waxman, M.D., Los Angeles, CA
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Neil Allen Weiner, M.D., Denver, CO
James David Weiss, M.D., Berkeley, CA
Vanessa Lynn Werlla, M.D., Tulsa, OK
Alan Christopher Whitters, M.D., Cedar Rapids, IA
Jaron Lerner Winston, M.D., Austin, TX
Nancy Claire Winters, M.D., Oregon City, OR
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Timothy Kane Wolff, M.D., Dallas, TX
Robin Eleanor Wragg, M.D., Pittsburgh, PA

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James Joseph Young, D.O., FPO Seattle, WA
Melinda L. Young, M.D., Redondo Beach, CA
Sean Hearn Yutzy, M.D., St. Louis, MO

John Michael Zimburean, M.D., Dallas, TX
Mark S. Zoccolillo, M.D., Amarillo, TX

NEUROLOGY

Ingrid Aina Abols-Mantyh, M.D., Edina, MN
Arnold J. Aguilera, M.D., Danville, PA
Mumtaz Ahmed Ali, M.D., Los Angeles, CA
Lancelot Oliver Alexander, M.D., San Diego, CA
Rajeswari Ananda, M.D., Westlake Village, CA
Merrill Ansher, M.D., Columbia, MD

Miles Jay Belgrade, M.D., Minneapolis, MN
Berta Maria Bergia, M.D., Knoxville, TN
Scott Malcolm Bergman, M.D., Palm Springs, CA
Nelson Antonio Berrios, M.D., Sugarland, TX
Carolyn Ruth Burkhardt, M.D., Denver, CO

Thomas John Chippendale, M.D., Encinitas, CA
Gregory Lynn Clark, M.D., Los Gatos, CA

Genet Barbara D'Arcy, M.D., Boulder, CO
Joel M. Dean, D.O., Grand Junction, CO
William Stephen Denson, M.D., Mobile, AL
Thomas Michael Duginski, M.D., Dixon, CA

John David England, M.D., Denver, CO

Bena Fisher, M.D., Saratoga, CA
John Francis Foley, M.D., Salt Lake City, UT
Michael Wilford French, M.D., Indianapolis, IN
Robert Freundlich, M.D., Malibu, CA
Robin Dell Fross, M.D., South San Francisco, CA

Douglas Roger Galasko, M.D., San Diego, CA
Tyson Robert Garrett, M.D., Vacaville, CA
William Washburn Gladney, Jr., M.D., Baton Rouge, LA
Karl Franz Gross, M.D., Aurora, CO

Allen Ching-Yang Han, M.D., Sioux Falls, SD
Jay Ronald Hess, M.D., Los Altos, CA
Robert Steven Hoffman, M.D., San Francisco, CA
Lawrence Ray Huntoon, M.D., Jamestown, NY

Marina Kasavin, M.D., San Francisco, CA
Brian John Kelly, M.D., Pleasanton, CA
Catherine Elizabeth Kenny, M.D., Colorado Springs, CO
Chan Kim, M.D., Fullerton, CA
Lung-Suen Kong, M.D., Camarillo, CA
Ingrid Louise Kwee, M.D., Moraga, CA
Pow Fah Kwo-On-Yuen, M.D., San Diego, CA

Stephen Hall Landy, M.D., Memphis, TN
Jorge Progreso Lipiz, M.D., Garden Grove, CA
Frank Michael Longo, M.D., San Francisco, CA
Daniel Henry Lowenstein, M.D., San Francisco, CA

Mehrdad Michael Mahdad, M.D., Huntington Beach, CA
Mayur Chandulal Maniar, M.D., Clarks Summit, PA
Joyce Elaine Mauk, M.D., Denver, CO
Joseph Henry Mayer, M.D., Willowbrook, IL
James McCurry Mays, M.D., Fort Collins, CO
Karl Edward Misulis, M.D., Nashville, TN

Marilyn Miller Newsom, Ph.D., M.D., Boulder, CO

Minoru Oishi, M.D., Suginami-ku, Tokyo, Japan
Jeffrey Leon Ortstadt, M.D., Deer Park, CA

Stuart W.H. Pang, M.D., Honolulu, HI
Thomas Arthur Phipps, M.D., Tualatin, OR
J. Steven Poceta, M.D., La Jolla, CA
Kevin Joseph Puzio, M.D., Indianapolis, IN

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Michael Charles Rowbotham, M.D., San Francisco, CA
Robert Phillip Rubens, M.D., Edmonds, WA

James Henderson Sabry, M.D., Menlo Park, CA
Robert L. Satake, M.D., Prairie Village, KS
Marc Hudson Schieber, M.D., St. Louis, MO
Zachary Simmons, M.D., Greenbelt, MD
Yuen Tat So, M.D., San Francisco, CA
Jeffrey David Steier, M.D., Paradise Valley, AZ
Aleksandra Antonina Stobnicki, M.D., Bannockburn, IL

Mark Henry Tuszynski, M.D., La Jolla, CA

David Gregg Vossler, M.D., Bothell, WA

Roi Ann Wallis, M.D., Valencia, CA
Chatree Wongjirad, M.D., Bismark, ND
Kelly G. Woodward, M.D., Oak Forest, IL

NEUROLOGY WITH SPECIAL QUALIFICATION IN CHILD NEUROLOGY

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Brian Edward Grabert, M.D., Colorado Springs, CO

Jin S. Hahn, M.D., San Diego, CA
Philip Jeffrey Holt, M.D., Atlanta, GA

Richard Aaron Kaplan, M.D., San Diego, CA
Joyce Alice Kobori, M.D., San Jose, CA

Jarlath Joseph Mitchell, M.D., Johnson City, TN

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Stephen Gregory Ryan, M.D., San Antonio, TX

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The following successfully completed the Board examination in September 1989.

CHILD AND ADOLESCENT PSYCHIATRY

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Ralph Stephen Albertini, M.D., Hanover, NH

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Christine Baron Ballester, M.D., Tampa, FL
Annette Aroxie Bazian, M.D., Farmington Hills, MI
John Paul Beck, M.D., Urbana, IL

Eugene Victor Beresin, M.D., Acton, MA
Robert Ira Berkowitz, M.D., Stanford, CA
Martha Anne Bird, M.D., Georgetown, KY
Carrie Marie Borchardt, M.D., Minneapolis, MN
Breck Gerard Borcherding, M.D., Frederick, MD
Janice Meyers Bow, M.D., St. Clair Shores, MI
Alta Lois Brubaker, M.D., Ithaca, NY
Richard Lee Burns, M.D., Prestonsburg, KY

Babette B. Caraccio, M.D., Cos Cob, CT
Ralph Lawrence Chester, M.D., Harahan, LA

Sheila Joyce Clark, M.D., Gadsden, AL
Charles Warren Coats, M.D., Greenwood, IN
Peter Ronald Cohen, M.D., Rockville, MD
Vincent Ricardo Collins, M.D., Hanover, NH
Don Condie, M.D., Boston, MA
Daniel Fredrick Connor, M.D., Boylston, MA
Steven Jay Cooper, M.D., Monsey, NY
Sara Louise Crowner, M.D., Pittsburgh, Pa

Mark DeAntonio, M.D., Los Angeles, CA
Bert Ludwig Dech, M.D., Port Washington, NY

James Edwin Deming, Jr., M.D., Sunrise, FL
Stephen Joseph Donovan, M.D., Jamaica, Queens, NY
David Downie IV, M.D., West Columbia, SC
Joseph Mark Drinka, M.D., Winter Park, FL

Mark David Edelstein, M.D., Sacramento, CA

Neil Joseph Fialkow, M.D., Evanston, IL
Aaron Harlan Fink, M.D., Houston, TX
Peter Mark Fink, M.D., Glenview, IL
Geraldine Susan Fox, M.D., Chicago, IL
Dickey Catherine Fuchs, M.D., Nashville, TN
Ruth Louvenia Fuller, M.D., Denver, CO

Theodore John Gaensbauer, M.D., Denver, CO
Robert Andrew George, M.D., Portland, OR
Janine Gordon, M.D., Eugene, OR
John Edward Gordon, M.D., Ann Arbor, MI
Olga Gutierrez, M.D., Santa Monica, CA
Alicia Guttman-Jodorkovsky, M.D., Baltimore, MD

John David Hamilton, M.D., Davis, CA
Ansar Mohamed Haroun, M.D., San Diego, CA
William Robert Hartnagel, M.D., New York, NY
William Patrick Hayes, M.D., Hopewell, NJ
William Michael Heffron, M.D., Lexington, KY
Masoud Seyed Hejazi, M.D., Greensboro, NC
Mary Margaret Hennessy, M.D., Austin, MN
Ellen Nystrom Herman, M.D., Austin, TX
Jerry Dale Heston, M.D., Memphis, TN
Andrew George Hinkens, M.D., Portland, ME
Michelle Hirsch, M.D., Riverdale, NY
Henry Joseph Horacek, M.D., Charlotte, NC

Heidi Jache, M.D., Marietta, OH
Susan Carol Jenkins, M.D., Rochester, MN
Hugh Frederick Johnston, M.D., Madison, WI
Paramjit Toor Joshi, M.D., Lutherville, MD

Gabriel Kaplan, M.D., Springfield, NJ
Jagannath P. Karambelkar, M.D., Pittsburgh, PA
David L. Kaye, M.D., Buffalo, NY
Margo Knapp, M.D., Brookline, MA

Simon Kravitz, M.D., Elkins Park, PA
Markus John Potter Kruesi, M.D., Bethesda, MD
Eric Warren Kuntz, M.D., Brooklyn, NY
Sureshbabu Kurra, M.D., Tappan, NY
Howard Marc Kurtzman, M.D., Greensboro, NC

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Stephen D. Mallary, M.D., Savannah, GA
Manuel G. Marinas, M.D., New York, NY
Herman William Martin, Jr., M.D., Atlanta, GA
Daniel Evan Mason, M.D., South Salem, NY
Edwards Usher McReynolds, M.D., Sugarland, TX
George Evan Mellos, M.D., Northville, MI
Werner Peter Metz, M.D., Worcester, MA
Thomas Mead Murphy, M.D., Topeka, KS
Barbara Bridges Murray, M.D., Madison, WI

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Powerful medicine
to stop intrusive thoughts and acts

Anafranil®
clomipramine HCl
Powerful tricyclic therapy for obsessive-compulsive disorder

▲ *Relieves obsessions and compulsions in OCD patients with or without concomitant depression*

Reduces anxiety-producing intrusive thoughts[1]

Reduces ritualized behavior[1]

▲ *Dual mode of action creates a unique treatment role*
Anafranil is believed to block the reuptake of serotonin and norepinephrine.[2,3]

▲ *Safety and tolerability demonstrated in over 20 years of worldwide use*

Symptoms are substantially reduced in 58% of patients.[4]

The most common adverse events are dry mouth, somnolence, tremor, dizziness, constipation, and ejaculatory failure. Anafranil may lower the seizure threshold. See Warnings and full Prescribing Information on page 4.

CIBA–GEIGY

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Anafranil®
clomipramine hydrochloride
Capsules
Prescribing Information

DESCRIPTION

Anafranil, clomipramine hydrochloride, is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Anafranil is available as capsules of 25, 50, and 75 mg for oral administration.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:

CH₂CH₂CH₂—N=CH₃ ·HCl

Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

Inactive Ingredients. D&C Red No. 33 (25-mg capsules only), D&C Yellow No. 10, FD&C Blue No. 1 (50-mg capsules only), FD&C Yellow No. 6, gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's relatively selective capacity to inhibit the reuptake of serotonin (5-HT) as compared to norepinephrine (NE) may be important.

Pharmacokinetics

Absorption/Bioavailability: CMI from Anafranil capsules is as bioavailable as CMI from a solution. The bioavailability of CMI from capsules is not significantly affected by food.

In a dose proportionality study involving multiple CMI doses, steady-state plasma concentrations (C_max) and area-under-plasma-concentration-time curves (AUC) of CMI and CMI's major active metabolite, desmethylclomipramine (DMI), were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C_max and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and CMI/DMI concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C_max and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of CMI occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/ml to 154 ng/ml (mean, 92 ng/ml). After multiple daily doses of 150 mg of Anafranil, steady-state maximum plasma concentrations range from 94 ng/ml to 339 ng/ml (mean, 218 ng/ml) for CMI and from 134 ng/ml to 532 ng/ml (mean, 274 ng/ml) for DMI. No pharmacokinetic data is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

Distribution: CMI distributes into cerebrospinal fluid (CSF) and brain and into breast milk. DMI also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of CMI is approximately 97%, principally to albumin, and is independent of CMI concentration. The interaction between CMI and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

Metabolism: CMI is extensively biotransformed to CMI and other metabolites and their glucuronide conjugates. DMI is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of CMI in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of CMI and DMI were only about 0.8-1.3% of the dose administered. CMI does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

Elimination: Evidence that the C_max and AUC for CMI and DMI may increase disproportionately with increasing oral doses suggests that the metabolism of CMI and DMI may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of CMI and DMI are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, CMI and DMI may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of CMI ranges from 19 hours to 37 hours (mean, 32 hr) and that of DMI ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for CMI. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for CMI is approximately 2.5 and for DMI is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of CMI and DMI (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of Anafranil have not been determined.

Pharmacokinetic Interactions: Coadministration of haloperidol with CMI increases plasma concentrations of CMI. Coadministration of CMI with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated CMI better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of CMI were significantly higher in smokers than in nonsmokers.

INDICATIONS AND USAGE

Anafranil is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of Anafranil for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking CMI experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. CMI treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of Anafranil for the treatment of OCD long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use Anafranil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Anafranil is contraindicated in patients with a history of hypersensitivity to Anafranil or other tricyclic antidepressants.

Anafranil should not be given in combination, or within 14 days of treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Anafranil is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS

Seizures

During premarket evaluation, seizure was identified as the most significant risk of Anafranil use.

The observed cumulative incidence of seizures among patients exposed to Anafranil at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates disc correct the crude rate (i.e., 0.7%, 25/3519) for the variable duration of exposure times among the patients who participated in the development program.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of CMI greater than 250 mg is limited, given that the plasma concentration of CMI may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Rare reports of fatalities in association with seizures have been recorded by foreign post-marketing surveillance systems over the 20 years of Anafranil's nondomestic marketing. In some of these cases, Anafranil had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions.

Caution should be used in administering Anafranil to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold. Physicians should discuss with patients the risk of taking Anafranil while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

PRECAUTIONS

General

Suicide: Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for Anafranil should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular Effects: Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking Anafranil in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with CMI in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

Psychosis, Confusion, And Other Neuropsychiatric Phenomena: Patients treated with Anafranil have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Anafranil. As with tricyclic antidepressants to which it is closely related, Anafranil may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

Mania/Hypomania: During premarketing testing of Anafranil in patients with affective disorder, hypomania or mania were precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to Anafranil.

Hepatic Changes: During premarketing testing, Anafranil was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

Hematologic Changes: Although no instances of severe hematologic toxicity were seen in the premarketing experience with Anafranil, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with Anafranil use. As is the case with tricyclic antidepressants to which Anafranil is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with Anafranil.

Central Nervous System: More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when Anafranil was used in combination with other drugs when Anafranil and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Sexual Dysfunction: The rate of sexual dysfunction in male patients with OCD who were treated with Anafranil in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

Weight Changes: In controlled studies of OCD, weight gain was reported in 18% of patients receiving Anafranil, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving Anafranil had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving Anafranil and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

Electroconvulsive Therapy: As with closely related tricyclic antidepressants, concurrent administration of Anafranil with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Surgery: Prior to elective surgery with general anesthetics, therapy with Anafranil should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

Use in Concomitant Illness: As with closely related tricyclic antidepressants, Anafranil should be used with caution in the following:

1. Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity.
2. Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug.
3. Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises.
4. Patients with significantly impaired renal function.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of Anafranil, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of Anafranil have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Anafranil:

1. The risk of seizure (see WARNINGS).
2. The relatively high incidence of sexual dysfunction among males (see PRECAUTIONS, Sexual Dysfunction).
3. Since Anafranil may impair the mental and/or physical abilities required for performance of complex tasks, and since Anafranil is associated with a seizures, patients should be cautioned about the performance of complex hazardous tasks (see WARNINGS).
4. Patients should be cautioned about using alcohol, barbiturates, or other depressants concurrently, since Anafranil may exaggerate their response to those drugs.
5. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
6. Patients should notify their physician if they are breast-feeding.

Drug Interactions

The risks of using Anafranil in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of Anafranil, caution is advised in using it concomitantly with other CNS-active drugs (see PRECAUTIONS, Information for Patients). Anafranil should not be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when Anafranil is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect might be anticipated because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of CMI has been reported to be increased by concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by concomitant administration of either methylphenidate, cimetidine, or fluoxetine and such an effect may be anticipated with CMI as well. Administration has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Pharmacokinetic Interactions).

Because Anafranil is highly bound to serum protein, the administration of Anafranil to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound Anafranil by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in doses 20 times the maximum daily human dose. Three out of 235 treated a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given approximately 5 times the maximum daily human dose.

Pregnancy Category C

No teratogenic effects were observed in studies performed in rats and doses up to 20 times the maximum daily human dose. Slight nonspecific effects were seen in the offspring of pregnant mice given doses 10 times maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken Anafranil until delivery. Anafranil should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Nursing Mothers

Anafranil has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In a controlled clinical trial in children and adolescents (10-17 years of age) outpatients received Anafranil for up to 8 weeks. In addition, 150 adolescent patients have received Anafranil in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years or less and 146 were 14-17 years of age. While the adverse reaction profile for this age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with Anafranil may have on the growth and development of children.

The safety and effectiveness in children below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of Anafranil in children under the age of 10.

Use in Elderly

Anafranil has not been systematically studied in older patients; but 152 patients at least 60 years of age participating in U.S. clinical trials received Anafranil for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

ADVERSE REACTIONS

Commonly Observed

The most commonly observed adverse events associated with the use of Anafranil and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

Leading to Discontinuation of Treatment

Approximately 20% of 3616 patients who received Anafranil in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received Anafranil in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving Anafranil (N=322) or placebo (N=319) or children treated with Anafranil (N=46) or placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials
(Percentage of Patients Reporting)

Body System/ Adverse Event*	Adults Anafranil (N=322)	Placebo (N=319)	Children Adolescents Anafranil (N=46)
Nervous System			
Somnolence	54	16	48
Tremor	54	2	33
Dizziness	54	14	41
Headache	52	41	28
Insomnia	25	15	11

Anafranil* clomipramine hydrochloride

Body System/ Adverse Event*	Adults Anafranil (N=322)	Adults Placebo (N=319)	Children and Adolescents Anafranil (N=46)	Placebo (N=44)
Libido change	21	3	—	—
Nervousness	18	2	4	2
Myoclonus	13	—	2	—
Increased appetite	11	2	—	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	2	—
Twitching	7	1	4	5
Impaired concentration	5	2	—	—
Depression	5	1	—	—
Hypertonia	4	1	2	—
Sleep disorder	4	—	9	5
Psychosomatic disorder	3	—	—	—
Yawning	3	—	—	—
Confusion	3	—	2	—
Speech disorder	3	—	—	—
Abnormal dreaming	3	—	—	2
Agitation	3	—	—	—
Migraine	3	—	—	—
Depersonalization	2	—	2	—
Irritability	2	2	2	—
Emotional lability	2	—	—	2
Panic reaction	1	—	2	—
Aggressive reaction	—	—	2	—
Paresis	—	—	2	—
Skin and Appendages				
Increased sweating	29	3	9	—
Rash	8	1	4	2
Pruritus	6	—	2	2
Dermatitis	2	—	—	2
Acne	2	2	—	5
Dry skin	2	—	—	5
Urticaria	1	—	—	—
Abnormal skin odor	—	—	2	—
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	—	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	—
Flatulence	6	3	—	2
Tooth disorder	5	—	—	—
Gastrointestinal disorder	2	—	—	2
Dysphagia	2	—	—	—
Esophagitis	1	—	—	—
Eructation	—	—	2	2
Ulcerative stomatitis	—	—	2	—
Body as a Whole				
Fatigue	39	18	35	9
Weight increase	18	1	2	—
Flushing	8	—	7	—
Hot flushes	5	—	2	—
Chest pain	4	4	7	—
Fever	4	—	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	—	—
Chills	2	1	—	—
Weight decrease	—	—	7	—
Otitis media	—	—	4	5
Asthenia	—	—	2	—
Halitosis	—	—	2	—
Cardiovascular System				
Postural hypotension	6	—	4	—
Palpitation	4	2	4	—
Tachycardia	4	—	2	—
Syncope	—	—	2	—
Respiratory System				
Pharyngitis	14	9	—	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	6
Bronchospasm	2	—	7	2
Epistaxis	2	—	—	—
Dyspnea	—	—	2	—
Laryngitis	—	1	2	—
Urogenital System				
Male and Female Patients Combined				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	—	—
Micturition frequency	5	3	—	—
Urinary retention	2	—	7	—
Dysuria	2	2	—	—
Cystitis	2	—	—	—
Female Patients Only	(N=182)	(N=167)	(N=10)	(N=21)
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	—	—	—
Menstrual disorder	4	2	—	—
Vaginitis	2	—	—	—
Leukorrhea	2	—	—	—
Breast enlargement	2	—	—	—
Breast pain	1	—	—	—
Amenorrhea	1	—	—	—
Male Patients Only	(N=140)	(N=152)	(N=36)	(N=23)
Ejaculation failure	42	2	6	—
Impotence	20	3	—	—
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	—	4	—
Tinnitus	6	—	4	—
Abnormal lacrimation	3	2	—	—
Mydriasis	2	—	—	—
Conjunctivitis	1	—	—	—
Anisocoria	—	—	2	—
Blepharospasm	—	—	2	—
Ocular allergy	—	—	2	—
Vestibular disorder	—	—	2	2
Musculoskeletal				
Myalgia	13	9	—	—
Back pain	6	6	—	—
Arthralgia	3	5	—	—
Muscle weakness	1	—	2	—
Hemic and Lymphatic				
Purpura	3	—	—	—
Anemia	—	—	2	2
Metabolic and Nutritional				
Thirst	2	2	—	2

Other Events Observed During the Premarketing Evaluation of Anafranil

During clinical testing in the U.S., multiple doses of Anafranil were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to Anafranil who experienced an event of the type cited on at least one occasion while receiving Anafranil. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with Anafranil, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: Infrequent — general edema, increased susceptibility to infection, malaise. Rare — dependent edema, withdrawal syndrome.

Cardiovascular System: Infrequent — abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. Rare — aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System: Infrequent — abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. Rare — cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System: Infrequent — hypothyroidism. Rare — goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System: Infrequent — lymphadenopathy. Rare — leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder: Infrequent — dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. Rare — fat intolerance, glycosuria.

Musculoskeletal System: Infrequent — arthrosis. Rare — dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

Nervous System: Frequent — abnormal thinking, vertigo. Infrequent — abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. Rare — anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

Respiratory System: Infrequent — bronchitis, hyperventilation, increased sputum, pneumonia. Rare — cyanosis, hemoptysis, hypoventilation, laryngismus.

Skin and Appendages: Infrequent — alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. Rare — chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

Special Senses: Infrequent — abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. Rare — blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

Urogenital System: Infrequent — endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, testis disorder, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. Rare — albuminuria, anorgasmy, breast engorgement, breast fibroadenosis/cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

DRUG ABUSE AND DEPENDENCE

Anafranil has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with Anafranil discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential Anafranil abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received Anafranil for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for Anafranil in foreign marketing, it is not possible to predict the extent to which Anafranil might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE

Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with Anafranil either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/mL. All 10 patients completely recovered. Among reports from other countries of Anafranil overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, CMI's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of Anafranil may not reflect the severity of poisoning; they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery. The slow intravenous administration of physostigmine salicylate has been reported to reverse the cardiovascular and CNS anticholinergic manifestations of tricyclic overdosage; however, it should not be used routinely, since it may induce seizures and cholinergic crises and there is persisting diabetic about its net utility.

In the alert patient, the stomach should be emptied promptly by induced emesis followed by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Lavage should be continued for 24 hours or longer, depending on the apparent severity of intoxication. Normal or half-normal saline should be used to avoid water intoxication, especially in children. Instillation of activated charcoal slurry may help reduce absorption of CMI.

External stimulation should be minimized to reduce the tendency for convulsions, and anticonvulsants may be necessary. If MAO inhibitors have been taken recently, barbiturates should not be used. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, dopamine, or dobutamine by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by, whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of Anafranil in tissues.

DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of Anafranil in 520 adults, and 91 children and adolescents with OCD. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both CMI and its active metabolite, DMI, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)

Treatment with Anafranil should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue Anafranil, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Anafranil after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

HOW SUPPLIED

Capsules 25 mg — ivory/melon yellow (imprinted ANAFRANIL 25 mg)
Bottles of 100 ....NDC 0083-0115
Unit Dose (blister pack)
Box of 100 (strips of 10)................................NDC 0083-0115
Capsules 50 mg — ivory/aqua blue (imprinted ANAFRANIL 50 mg)
Bottles of 100 ....NDC 0083-0116
Unit Dose (blister pack)
Box of 100 (strips of 10)................................NDC 0083-0116
Capsules 75 mg — ivory/yellow (imprinted ANAFRANIL 75 mg)
Bottles of 100 ....NDC 0083-0117
Unit Dose (blister pack)
Box of 100 (strips of 10)................................NDC 0083-0117

Do not store above 86°F (30°C). Protect from moisture.

Dispense in tight container (USP).

ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with Anafranil. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

C9

*Events reported by at least 1% of Anafranil patients are included

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replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

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Letters to the Editor. Brief letters (maximum of 500 words and 5 references; no tables or figures) will be considered if they include the notation "for publication." Letters critical of an article published in the *Journal* will automatically be sent to the authors for reply. Because of space limitations not all letters can be printed. The *Journal* will notify authors about the disposition of their letters but does not return those that are not published. A letter must be signed by all of its authors. All letters will be edited; edited letters will not be sent to authors for approval. Letters must be typed **double-spaced** throughout on $8\frac{1}{2} \times 11$ inch paper; three copies are required. Letters that do not meet these specifications will be returned for revision. Reprints are not available. **Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. Case reports submitted as Letters to the Editor will be peer reviewed.**

Book Forum. Books for review may be sent to the Book Forum Editor, Nancy C. Andreasen, M.D., Ph.D., University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242. Book reviews are usually solicited by the Book Forum Editor. Authors interested in reviewing a particular book should communicate directly with Dr. Andreasen. Reprints of reviews are not available.

TYPING AND ARRANGING THE PAPER

All parts of the manuscript, including case reports, quotations, references, and tables, must be **double-spaced** throughout. Manuscripts must be typed in upper- and lowercase on one side only of $8\frac{1}{2} \times 11$ inch **nonerasable** bond paper. All four margins must be $1\frac{1}{2}$ inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered.

STYLE SPECIFICATIONS

Title Page

Title. The title should be informative and as brief as possible. Two-part titles should be avoided.

By-line. Authors listed in the by-line should be limited to principal researchers and/or writers; collaborators may be acknowledged in a footnote. Authors' first names are preferred to initials. Degrees should be included after each author's name.

Previous presentation. If the paper has been presented at a meeting, please give the name of the meeting, the place, and the date.

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Acknowledgments. Grant support should be acknowledged in a separate paragraph and should include the full

name of the granting agency and grant number. The *Journal* does not allow acknowledgment of persons involved with the preparation or typing of manuscripts. Acknowledgment of individuals involved with the scientific content of the work should not exceed four typed lines. Drug company support of any kind must be acknowledged.

Abstract

The abstract is a single paragraph no longer than 100 words for Special Articles and Regular Articles and no longer than 40 words for Clinical and Research Reports.

Text

Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

Research design and statistics. The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. All significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3$, 17, $p< 0.05$)." Reviewers will evaluate the appropriateness of the analyses.

Abbreviations. Spell out all abbreviations (other than those for units of measure) the first time they are used. Idiosyncratic abbreviations should not be used.

Drugs. Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

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References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. Do **not** arrange the list alphabetically. References in tables and figures are numbered as though the tables and figures were part of the text.

References should be restricted to closely pertinent material. **Accuracy of citation is the author's responsibility.** References should conform exactly to the original spelling, accents, punctuation, etc. Authors should be sure that all references listed have been cited in text.

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1. Noyes R Jr, DuPont RL Jr, Pecknold JC, et al: Alprazolam in panic disorder and agoraphobia, results from a multicenter trial, II: patient acceptance, side effects, and safety. Arch Gen Psychiatry 1988; 45:423–428
2. Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987

TABLES AND FIGURES

The *Journal* does not publish tables or figures that have been submitted elsewhere or previously published. Tables and figures that duplicate 1) material contained in text or 2) each other will not be used. Authors will be asked to delete tables and figures that contain data which could be given succinctly in text. Each table and figure should be understandable without reference to the text; a descriptive, concise title should be included and units of measurement should be specified. Consult recent issues of the *Journal* for format. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. **A copy of each table and figure must be included with each copy of the manuscript.**

Tables

Tables should be double-spaced, no wider than 120 typewriter characters, including spaces, and no longer than 70 lines. Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given.

Figures

Figures are considered as text and are subject to revision by the authors upon recommendation of the Editors. Figures should, however, be professionally prepared. Glossy or other camera-ready prints should accompany the submitted manuscript. Computer-generated figures that do not meet quality printing standards will be returned for revision. The first author's name, the title of the paper, the figure number, and the top of the figure should be noted on a label affixed to the back of each figure. All figure titles and footnotes should be typed and sent together on a separate page.

The *Journal* does publish color illustrations. However, the cost to publish them, including reprint charges, will be the responsibility of the authors. An estimate of the cost will be provided to the authors at the time of first decision.

Format. Figures are visual expressions of data trends or relationships. Figures that represent numerical data which could be expressed more succinctly or clearly in tabular form should be converted to tables. Line graphs should show change in continuous variables; comparisons of like values in different groups should be presented as bar graphs. Graphs containing stacked bars are unacceptable; the different segments of each bar should be presented side by side.

Lettering. Figure type should be sans serif and should be 7 points or larger after the figure is reduced; most figures taking up the width of a vertical manuscript page are reduced to a width of 19.5 picas (3¼ inches), and those requiring a horizontal manuscript page are usually reduced to 40.5 picas (6¾ inches). When space on the horizontal axis is insuffi-

FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects

[a]Significant difference between men and women (t=1.81, df=10, p<0.05) and between the total Alzheimer's disease group and the total control group (t=2.49, df=25, p<0.01).
[b]Significant difference between the total depressed group and the total control group (t=2.75, df=33, p<0.005).

cient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

Other. The following are additional specific requirements. Please refer to the example given above.

1. Do not use solid black shading; rather, include outlined white among shadings.

2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.

3. Error bars should not be used.

4. Do not extend the vertical or horizontal axis of a graph beyond the point needed for the data shown.

5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.

6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.

7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).

8. The key should appear within or above the figure but should not be wider than the figure itself. Avoid placing other type (e.g., number of subjects, statistical values) within the axes of a graph.

9. Footnotes (including p values) should be cited with superscript letters in the title or body of the figure and should be listed in the order in which they are cited in the figure.

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HOPE BEGINS WITH SUPERIOR SYMPTOMATIC CONTROL*

In a six-week controlled study in severely ill ("problem") schizophrenic patients who failed to respond adequately to treatment with appropriate courses of standard antipsychotic drugs:

- CLOZARIL® (clozapine) succeeded after standard antipsychotics, including haloperidol, failed

- Thirty percent of CLOZARIL patients experienced dramatic global improvement in only six weeks (as determined by the study's rigorous efficacy criteria) vs only 4% of patients receiving chlorpromazine

- Efficacy in both positive and negative symptomatology

HOPE CONTINUES WITH A VIRTUAL ABSENCE OF CERTAIN ACUTE EXTRAPYRAMIDAL SYMPTOMS

- CLOZARIL® (clozapine) is indicated for patients intolerant of standard antipsychotics

- No confirmed cases of tardive dyskinesia in over 15 years' worldwide experience

- Side effects that have been reported include: agranulocytosis (1–2%), transient sedation (39%), hypersalivation (31%), tachycardia (25%), constipation (14%), hypotension (9%), hypertension (4%) and weight gain (4%)†

- CLOZARIL use is associated with a substantial risk of seizure, an apparently dose-dependent reaction affecting 1–2% of patients at low doses (below 300 mg/day), 3–4% at moderate doses, and 5% at high doses (600–900 mg/day)‡

HOPE IS MAINTAINED THROUGH A MANDATORY WBC MONITORING SYSTEM WHICH HELPS MANAGE THE RISK OF AGRANULOCYTOSIS

- Agranulocytosis, a potentially fatal disorder, occurs in 1–2% of patients

- The Clozaril Patient Management System℠ (CPMS℠) was created as an efficient means to detect developing agranulocytosis

- This structured weekly monitoring and drug delivery system helps to protect the patient and to support the physician

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(clozapine)

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*In a double-blind study of CLOZARIL (clozapine) versus chlorpromazine encompassing 268 patients, all of whom had first failed on at least three standard antipsychotics over a five-year period and then

CLOZARIL®

(clozapine)
TABLETS

CAUTION: Federal law prohibits dispensing without a prescription.

CONTRAINDICATIONS

CLOZARIL is contraindicated in patients with myeloproliferative disorders, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. CLOZARIL should not be used simultaneously with other agents having a well-known potential to suppress bone marrow function. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

WARNINGS

General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZARIL MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR FOUR WEEKS AFTER THE DISCONTINUATION OF CLOZARIL.

CLOZARIL IS AVAILABLE ONLY THROUGH THE CLOZARIL PATIENT MANAGEMENT SYSTEM℠ (CPMS℠).

Agranulocytosis

Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm³, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1986, 35% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.

Treatment should not be initiated if the WBC count is less than 3500 per mm³, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm³ or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm³, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm³ and a granulocyte count above 1500 per mm³, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000 per mm³ or the granulocyte count below 1500 per mm³, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm³ and the granulocyte count returns to levels above 1500 per mm³. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm³.

If the total WBC count falls below 2000 per mm³ or the granulocyte count falls below 1000 per mm³, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000 per mm³, or granulocyte counts below 1000 per mm³ during CLOZARIL therapy should *not* be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).

Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.

To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.

Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL.

CLOZARIL® (clozapine) TABLETS

Drug Interactions

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function. Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs. Because CLOZARIL is highly bound to serum protein, the administration of CLOZARIL to a patient taking another drug which is highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL by other highly bound drugs.

CLOZARIL may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

ADVERSE REACTIONS

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of 5% or greater were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

DOSAGE AND ADMINISTRATION

Initial Treatment

It is recommended that treatment with CLOZARIL begin at 25 mg once or twice daily, and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of two weeks. Subsequent dosage increments should be made no more than once- or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL in treatment resistant patients, the mean and median CLOZARIL doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

Discontinuation of Treatment

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1 to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

CLOZARIL is available only through the Clozaril Patient Management System, a program that combines white blood cell testing, patient monitoring, pharmacy, and drug distribution services, all linked to compliance with required safety monitoring.

To prescribe CLOZARIL call 1-800-237-CPMS (2767) or mail in a completed CPMS Enrollment Form.

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For IM Injection Only

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL Decanoate 50 and HALDOL Decanoate 100 are attributed to HALDOL haloperidol as the active medication. Contraindications, Warnings, and additional information are those of HALDOL, modified to reflect the prolonged action.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS—Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS—Drug Interactions)

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

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